SEPTEMBER 1959
VOL. XX No. 3

# Circulation

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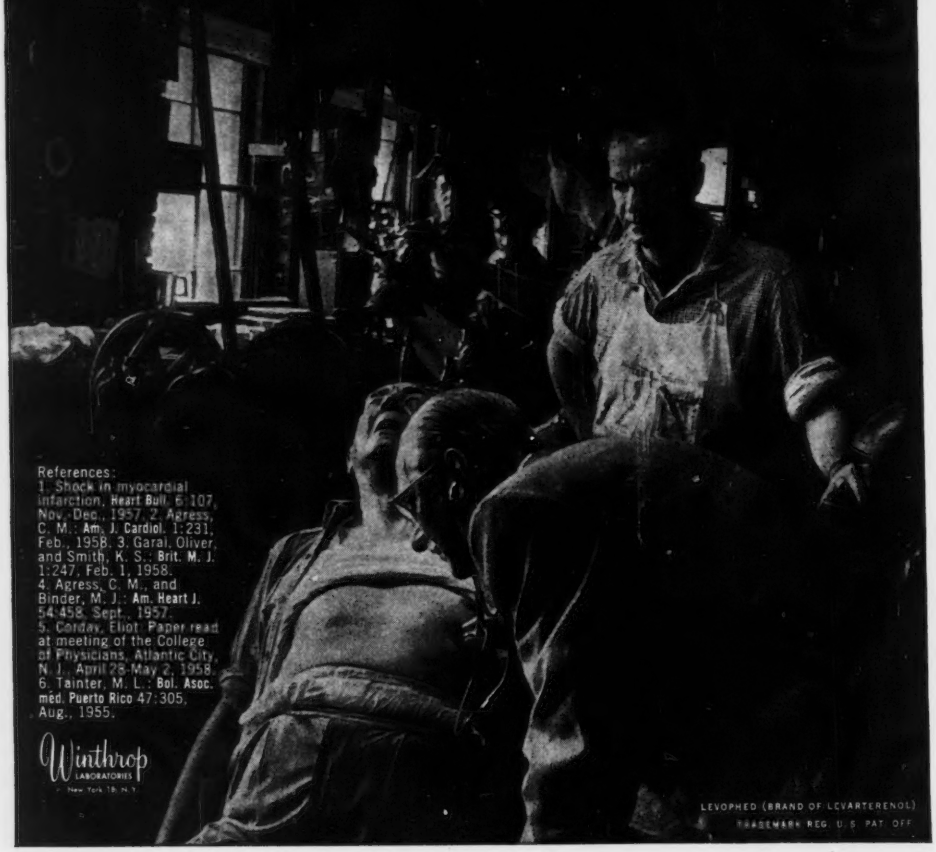

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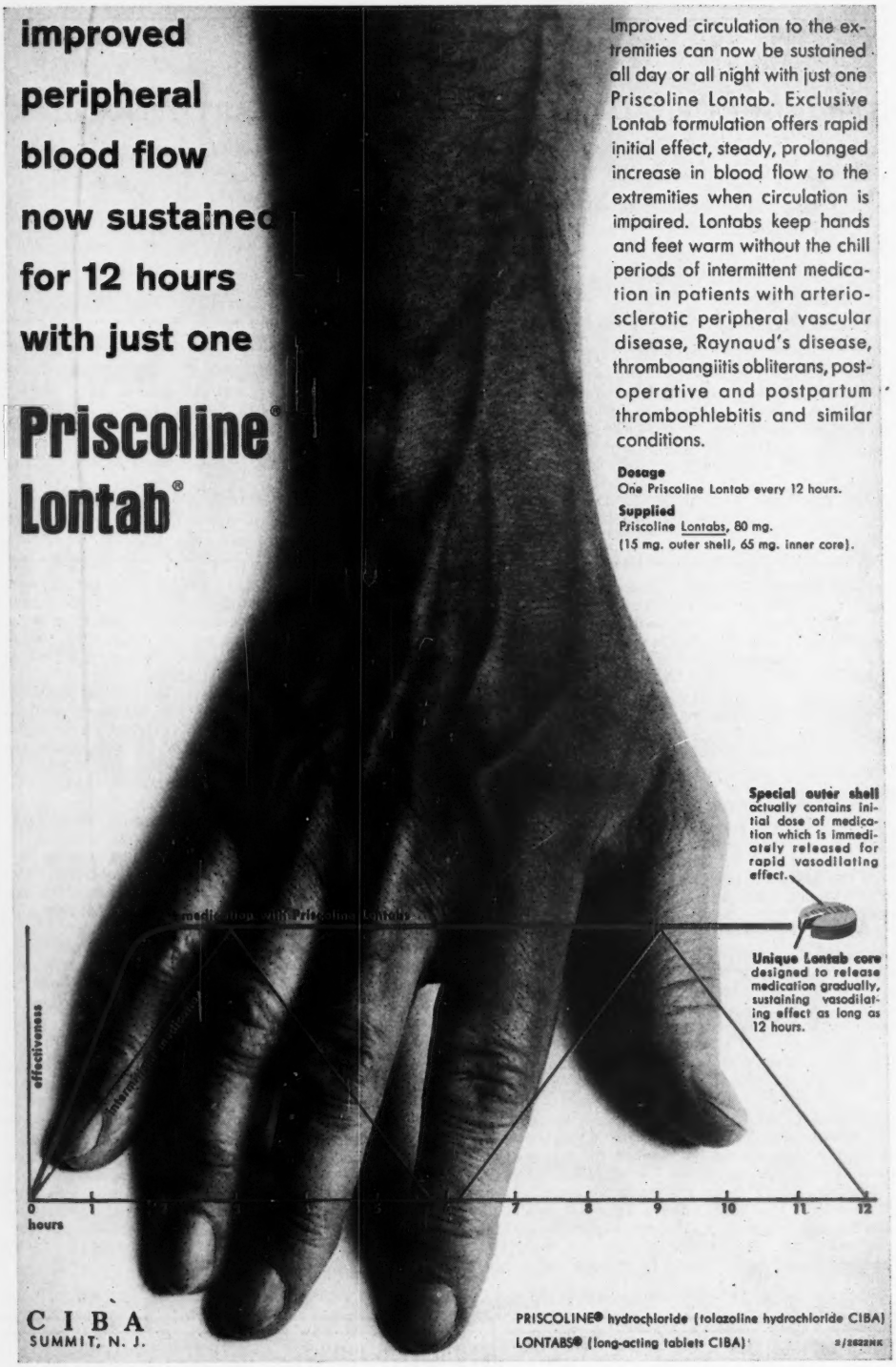
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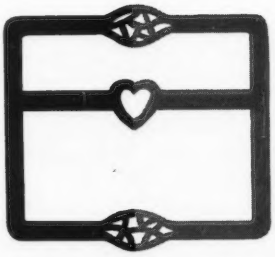

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# Editorial

## Clinical Science, Clinical Medicine, and Academic Medicine

IN A notable series of 4 lectures including a Harveian Oration and a Huxley Lecture, presented at intervals between 1930 and 1935,[1-4] the late Sir Thomas Lewis discussed the role of research in medicine with special reference to what he called clinical science (a term resurrected from Paget) and its relationship to academic medicine and clinical medicine. He called Harvey the founder of clinical science and said that the work of Ferrier, Horsley, Mackenzie, and Head further illustrates what is meant by it. Clinical science seeks to define diseases in man and to understand these diseases and their manifestations, by both observation and use of the experimental method; it establishes a linkage between practical medicine and physiology and pathology by workers who have the necessary training and sufficient leisure to understand and apply the knowledge these sciences are gaining; overlaps among clinical science, pathology, and physiology are vital to medical science as a whole. Young men whose life work lies in clinical medicine should not be made to feel that clinical research is less fruitful than physiologic research. Before World War I there was little financial support for clinical science but more recently at least some private and governmental sources of aid had become available.

Sir Thomas recommended that departments of clinical science be established in universities and that young men who had already demonstrated their capacities as experimenters or who gave promise of doing so be chosen to head such departments. He regarded the first duty of a university professor to be advancement of knowledge of his subject by research and the second to be encouragement and dissemination of learning. The focus of academic medicine must not be allowed to become the teaching of professional objectives to masses of students; the focus must be the fostering of pure learning.

Three divergencies between clinical science and curative medicine were pointed out: 1. Diagnosis is an end point of one and the starting point of the other. 2. Curative medicine deals with the individual but progressive medicine, i.e., clinical science, is collective in its outlook. 3. Profound and far-reaching intellectual divergencies in manners of thought and standards of accuracy exist. In curative medicine solutions are reached in by far the greatest number of instances by no process of logical reasoning but upon the basis of previous experience or by intuition. Because the physician must decide frequently upon an insecure basis of fact or argument, many of his decisions are frankly opportunist and many are wrong. If a problem of mechanism of disease presents itself, the physician's mind is torn from this problem to consider other problems before a clear line of thought can be established or followed to a satisfactory conclusion. The practice of medicine is destructive of consecutive thought; its continued practice weakens the very power to think consecutively and therefore clearly upon problems relating to the nature of disease.

Much water has flowed under the bridges in the comparatively short time since Sir Thomas

advanced the views summarized above. We are increasingly aware that future progress in clinical medicine as well as in the biologic sciences, including the basic medical sciences, is largely dependent upon advances in fundamental sciences such as physics and chemistry. Thus the linkages of clinical science need to be extended far beyond physiology and pathology and frequently beyond the conventional scope of medicine. Clinical scientists today have a far broader range for their activities.

The present-day financial support of medical research, in this country at least, is probably far greater than anything Sir Thomas had in mind when he complained of such matters in Britain nearly a generation ago. The funds expended for medical research in 1940 were $45,000,000 and in 1957, $330,000,000.[5] It is estimated that by 1970 between $900,000,000 and $1,000,000,000 will be expended. The relative contribution of various government agencies was 7 per cent in 1940 and 56 per cent in 1957. The current program is said to be staffed by 20,000 professional medical research scientists but it is estimated that by 1970, 45,000 will be employed. The additions to the medical research manpower pool are expected to include from 16,000 to 20,000 scientists with the Ph.D. degree and 6,300 physicians although most of the latter will carry on part-time research.

The term "medical research" as employed in connection with the figures stated above includes the basic medical sciences and related biological sciences, clinical research, industrial medical research such as that carried on by the pharmaceutical industry, and projects dealing with social and economic phases of medicine. Certain teaching and training activities also appear to be included. The amount of funds and manpower directly devoted to what Sir Thomas would have called clinical science can scarcely be estimated, but it is clear that both have been greatly increased.

The new frontal assault upon various problems of medicine has already subjected curative medicine to technologic changes requiring intensive propagation of new knowledge to practitioners and increase in specialization. Sir Thomas' blast at curative medicine, perhaps already out-dated when it appeared, has little bearing on the practice of clinical medicine today. A good clinician must be able to formulate hypotheses, test them, and make necessary adaptations and changes as he goes along. That is his process of "consecutive thinking." If he does not employ experience and intuition for what they are worth, it is his loss. He often has to construct his hypotheses with more gaps in the data than he might like. If he or the clinical scientist carries the process of consecutive thinking too many steps beyond his tests, each, if we may judge from what has happened in the past, is in similar danger of going astray.

The major objective of Sir Thomas in his lectures was to help clinical science achieve what he conceived to be its proper place as an entity in medicine under the guidance of what now might be called career investigators trained for that purpose. Although research in what Sir Thomas would have included in clinical science has increased greatly, it has been outstripped by the vast outlay for technologic research toward which pharmaceutical companies alone in this country are reported to have allotted $88,000,000 in 1957.[5] Moreover, practitioners in general are interested mainly in technologic research because they have found it more immediately useful for improving their diagnostic and therapeutic powers. There is, however, no water-tight compartment between the two types of research; findings obtained in technologic studies may open the door to progress in clinical science and to the better understanding of disease processes. The desirability of fostering investigation in clinical science, although already well understood in this country by limited groups of workers long before Sir Thomas' lectures were published, has slowly received more widespread recognition. The policy of the Research Committee of the American Heart Association should add impetus to this movement and, one may hope, encourage other

ommittees responsible for the allocation of unds to support research in clinical science ore liberally.

One does not have to disagree with Sir homas' principal thesis to conclude that clinal science is where you find it. He conceded at clinicians had contributed to clinical ience despite what he had to say about practice. But he pointed out that we were getting ose to the finish of being able to make important contributions by observations without xperiments. Great clinicians and clinical ientists like Heberden, Addison, and Potain reated their own opportunities, the like of which may or may not be present today. But ur present generation of clinicians have not been giving too bad an account of themselves. One has only to look about to see what they have done to increase knowledge of cardiovascular disease in the short time since the technologic triumph of cardiac surgery has been achieved and studies of the effects of recently developed antihypertensive measures have been undertaken. Technologic research and clinical science have been almost inextricably bound together in these developments.

Clinicians occupy a strategic position sometimes overlooked by those who write about how medical research should be done and who should do it. Clinicians are close to the raw material of clinical science. They sit by the bed side, agonize over the patients who look to them for help, and ask themselves questions that might not occur to the most analytical career investigators. In the past, such questions have constituted an important source of stimulation to clinical science as well as technologic research. One wonders whether Addison and Mackenzie would have done as well as full-time career investigators.

Sir Thomas' idea of what the focus of academic medicine should be was not clarified by a precise definition of "pure learning." It is obvious that he thought the focus should not be technology and "practical" training so popular today. He seemed to be equating pure learning with a knowledge of the basic sciences and clinical science, leading to an understanding of the causes and nature of diseases and the disturbances in body mechanisms produced by them. Much that was thought to be pure learning 2 generations ago is now gathering dust among the archives of medical history, a fate doubtless in store for some of the pure learning of today. Our students are subject to the same technologic inundation as practitioners and must learn many more clinical facts and many more "professional objectives." But they must also learn more about our greatly expanded basic sciences. The need to be critical, discriminating, and resourceful becomes more urgent. The cultivation of these qualities obviously requires an adequate background of the scientific and technologic factual material that our devoted, hard pressed medical faculties present to their students. But it also requires facility in the employment of logical processes of thought, which seems as essential to clinical medicine as to clinical science, despite Sir Thomas' view to the contrary. It is not only such great matters as advances in science that are based primarily upon inductive reasoning but even such everyday affairs as clinical diagnosis. Obviously the ability to employ deduction without constant blundering is equally necessary. We seem to require frequent reminders that mathematical procedures including statistical manipulations do not repeal the laws of logic; that one must not only be on guard with respect to stated assumptions but must look for those which are implied or even unsuspected; and that statisticians may not recognize whether data presented to them are appropriate for statistical treatment. The hazard of unsuspected bias, the pitfalls of improperly designed experiments, and the ease with which unsophisticated readers can convert a double-blind to a triple-blind group, need to be recognized. These are samples of a type of learning required by physicians that will not quickly become obsolete. Such matters might well be a concern of academic medicine instead of a corporal's guard of teachers.

If research in clinical science is to be encouraged, a supply of productive clinical

scientists seems essential. It would be difficult for a force of 20,000, to be increased to 45,000 by 1970, to engage in medical research, no matter how strictly much of it may be regimented in technologic channels, without some benefit to clinical science. But clinicians have been the great contributors to clinical science in the past, and as suggested above, there are important areas of investigation that have been their special province. Our most promising reservoir for future clinical scientists appears to be the intellectual elite among those beginning training in clinical medicine.

Plato warned us quite some time ago that in a democracy, the process of equality is visited upon the equal and the unequal. Our superior students must usually still conform to the leveling process of democratic education today, marching in step with the dull witted, thus having sacrificed for them at least 1 or 2 of the golden years that later should rightfully be theirs, even before they enter college. Another road block, not so widely perceived, appears in the early postgraduate years in the form of certifying boards, which, no matter how excellent their intentions and objectives, also enforce the leveling process upon those who have already learned much medicine as well as those who have not. Our superior medical residents whom we would like to have get on with projects worthy of their steel and who could easily meet the board requirements in one third of the equal training period demanded of them and their intellectually less agile brethren, have squandered for them a couple more of the golden years while they learn from experience how the law of diminishing returns operates. For such reasons, some of our potential clinical scientists have reached an age when they have given hostages to fortune and acquired an interest in security before they are ready to embark upon an uncertain and now less tempting enterprise. Others appear to have been on the receiving end of intellectual pabulum long enough to dull the priceless enthusiasm, energy, and initiative of the golden years, but there are always some able to rise superior to obstacles. Perhaps clinical science will benefit by having only the tough fibered, who cannot be turned aside, carry its banner, even though they might carry it farther, if they could start sooner. One may hope that the new "Plan H" of the American Board of Internal Medicine will help at least a few to start sooner.

CHARLES C. WOLFERTH

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# Editorial

## Heart Disease in India

ELSEWHERE in this issue is a report on cor pulmonale by one of India's leading cardiologists Dr. S. Padmavati, Professor of Medicine at the Lady Hardinge Medical College in New Delhi. The prevalence of the different types of heart disease in other countries and their clinical characteristics as compared with experience in one's own country is of great interest. Important insight is often afforded by such epidemiologic data.

On the basis of personal visits and ward rounds in hospitals in Calcutta, Lucknow, Agra, New Delhi, and Bombay, as well as from discussions with leading cardiologists and published reports from these centers, one gains certain impressions. These impressions are subject to revision as more reliable data become available. Currently available vital statistics from India are inevitably incomplete and approximate. The patients observed in the hospitals are a preselected group, representing in general the most desperately ill and those who are of the lower economic classes.

Rheumatic heart disease seems about as prevalent as in America. A clinical history of acute rheumatic fever is obtained in fewer patients with rheumatic valvular heart disease than in this country. In India rheumatic heart disease is responsible for 95 per cent of heart disease in children and for more than 25 per cent of heart disease seen in adults.[1, 2] Atherosclerotic cardiovascular disease is observed in a surprising number of cases and, as in our clinics, acute myocardial infarction is seen occasionally in the fourth decade in the absence of diabetes, hypertension, or other evident predisposing causes.

Of greatest interest is the prominence of chronic or subacute pulmonary heart disease, i.e., cor pulmonale. In Calcutta, Lucknow, and New Delhi approximately 20 per cent of all cardiac patients admitted to the hospital suffered from cor pulmonale. The percentage in some reports varies markedly because of differing criteria; in Bombay only 10 per cent are reported. It was found in children and young adults as well as in older persons. Thus of 1,250 cardiac cases admitted to the King George Medical College Hospital in Lucknow 34 per cent were rheumatic, 12 per cent hypertensive, and 10 per cent had myocardial infarction; 20 per cent were admitted because of cor pulmonale.[2] In Agra, K. S. Mathur observed 347 cases of chronic pulmonary heart disease, or 19 per cent, among 1,825 cases of organic heart disease.[3]

Cor pulmonale as observed in India contrasts sharply in several respects with experience in the United States. Initially the patients generally have no evidence of primary pulmonary disease by x-ray or clinically, except for chronic bronchitis with cough. The only physical signs may be moist or musical rales for months or a few years. The clinical course may be protracted over a decade or more; not infrequently, however, the patient may progress to generalized anasarca and death within a year or two.

Children and young adults as well as older subjects may be affected. These patients showed no evidence of rheumatic, syphilitic, or atherosclerotic heart disease. Particularly tragic were the adolescents dying in general anasarca. Pulmonary emphysema is usually not seen until the disease has progressed into advanced stages. Thus, in the series of 347 cases of cor pulmonale studied by K. S. Mathur, chronic bronchitis with emphysema was present in 85 per cent.

The etiology of the condition is not certainly known. It was not related to nutritional deficiency or kwashiorkor. Most of the patients were inhabitants of villages. This raises the possibility that the condition may be due to the inhalation of the irritating

smoke in the villages where cow dung is used in all cooking fires, and flocking around the fire during the winter is common. The smoke is evident everywhere in the city. Visitors, though sojourning away from the most densely populated areas of a city, frequently develop a dry, hacking, chronic cough. In certain cities such as Lucknow this "smog" is not dissimilar to that which pervades Los Angeles and some industrial areas in England. The chemical characteristics of the "smog" in various centers in India merit immediate attention. Extensive pathologic studies of the lungs also may be expected to afford additional insight. Investigation may reveal that the illness often is due to a chemical pneumonitis similar to nitrogen dioxide pneumonia, "silo-filler's disease" or "farmer's lung."[4, 5] In other cases the high rate of pulmonary infections, inadequately treated because of poverty and lack of medical facilities, may well play an important role.

HERRMAN L. BLUMGART

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The discovery of Laennec of the art of auscultation, by which, through changes in the normal sound within the chest, various diseases of the heart and lungs could be recognized, gave an immense impetus to clinical research. The art of percussion, discovered by Auenbrugger in the eighteenth century, and reintroduced by Corvisart, contributed not a little to the same. Laennec's contributions to the study of disease of the lungs, of the heart, and of the abdominal organs really laid the foundation of modern clinical medicine. WILLIAM OSLER.—*Aequanimitas and Other Addresses.* Blakiston & Co., Philadelphia, and T. K. Lewis, London, 1904.

# Congenital Cardiovascular Anomalies in Twins

*By* LUCILLE J. ROSS, M.D.

An attempt was made to derive information about the types of mechanisms that can produce congenital cardiovascular anomalies from a study of twins. The presence or absence of a cardiovascular malformation in the twins and in their siblings, and the zygosity of each twin pair were determined.

GREAT advances have been made during the past 2 decades in methods of diagnosing congenital cardiovascular lesions, and in concepts and technics of their surgical correction. There has been almost no progress, however, in the prevention of such defects because of the paucity of knowledge about their causes. The anomalies in humans appear to be genetically determined in certain instances and to be caused by an agent, such as the rubella virus, in the intrauterine environment on occasion; but in the majority of cases the etiologic factor is not known. It was hoped that a study of twins with congenital cardiovascular disease might clarify the cause of the anomalies, since twins are thought to be exposed to a relatively similar intrauterine environment, and monozygotic twins have an extremely similar genetic endowment.

A number of twins with congenital cardiovascular disease have been described. Unfortunately, at the time that some of the reports were written, the criteria for determining both the zygosity and the presence or absence of cardiovascular lesions were less rigid than currently. Table 1 summarizes the literature describing those pairs for which the diagnosis of zygosity seems valid. They have been divided into monozygotic pairs (those derived from 1 fertilized ovum) and dizygotic pairs (those derived from 2 fertilized ova). Table 1 also indicates which references describe twin pairs that were concordant for congenital cardiovascular disease (both co-twins affected), and which report discordant pairs (only 1 twin of the pairs had congenital heart disease).

From the Bureau for Handicapped Children, the City of New York Department of Health, N. Y.

Separate mention is made of twins having dextrocardia, either with[43–47] or without[48–56] another cardiac anomaly. Doolittle[44] reported 2 opposite-sex pairs; all the others were same-sex pairs. Three pairs[45, 49, 50] were concordant for dextrocardia.

Uchida and Rowe[57] reported the first study of a series of twins with congenital heart disease. Following rigid criteria in determining zygosity, they observed 13 monozygotic and 13 dizygotic pairs. Only 1 member of each of their twin pairs was affected.

## METHODS

A number of individuals associated with different health agencies throughout New York City suggested possible subjects for this investigation. Those twin pairs for which the zygosity could be determined and the presence or absence of a congenital cardiovascular anomaly could be established for each twin, were selected for inclusion in this study. The cases therefore do not represent a statistically random sample, and consequently the number of dizygotic pairs should not be compared with the number of monozygotic pairs, nor should the proportion of concordant pairs in each group be considered.

Insofar as possible, the investigation of each twin pair included the following data:

### *History*

*Family History.* The family history was obtained from one or both parents, with particular inquiry about multiple births, congenital abnormalities in any relative, and consanguinity. The mother's gynecologic and obstetric history was elicited with emphasis on menstrual irregularities, abortions, prematurely born babies, and complications of pregnancies or deliveries. The mother was asked specifically whether she had, to her knowledge, any chronic anemia; pulmonary, renal, cardiovascular, thyroid, or psychiatric disease; and whether she had ever received radiotherapy. Only superficial inquiry was made about the father's health; we did not routinely ask about irradiation of the father.

TABLE 1.—*Review of Literature on Twins with Congenital Cardiovascular Lesions*

| Probable zygosity | Criteria upon which zygosity-determination was based | Bibliographic references to: Probably concordant pairs | Bibliographic references to: Probably discordant pairs |
|---|---|---|---|
| Dizygotic | Opposite-sex | 2 | 1, 3, 4, 5 (3 pairs), 6 |
| | Physical differences or authors' statement | 5, 10, 11 | 5 (3 pairs), 7, 8, 9, 12-16 |
| Monozygotic | Monochorionic | 9, 19 | 17 (2 pairs), 18, 20 |
| | Similarity of many blood types and of physical appearance | | 14 (2 pairs), 21, 22 (2 pairs), 23, 24, 25 (2 pairs) |
| | Similarity of appearance | 31, 32, 33 | 5 (7 pairs), 8, 26-30 |
| | Authors' statement: "Identical" | 34-39 | 14 (2 pairs), 38, 40, 41, 42 |

*History of the Twin Gestation.* Information about the twin pregnancy and delivery was obtained from the mother or hospital medical records. Mothers were questioned about excessive nausea or vomiting, vaginal bleeding, uterine cramps, medications (other than vitamins, calcium, or iron), surgery, any unusual psychogenic factors, infections, contact with the common contagious diseases, herpes simplex, immunization against poliomyelitis (in those pregnancies that occurred after the introduction of the Salk vaccine), and vaccination against smallpox. Medical records were examined for evidence of toxemia[58] and the results of serologic tests. Information about the maternal blood types was available in only some instances, and about the hemoglobin in very few.

In the case reports, absence of a statement about any of the above facets of the history indicates that information was available and was negative. To avoid repetition, only positive information, or where appropriate, a comment that the information was incomplete, has been included.

*Cardiac Evaluation*

A physical examination of the cardiovascular system of the (living) twins and of their full siblings was performed by the author, unless a statement to the contrary appears in the case report. Electrocardiographic and roentgenographic findings and the descriptions of angiocardiograms, the results of cardiac catheterization, surgical procedures, and postmortem examinations were usually obtained from hospital or clinic medical records.

The co-twins and siblings were examined for cyanosis and clubbing, and auscultation of their hearts was performed. Peripheral pulses were palpated in the lower extremities or the blood pressure was measured. The absence of a remark about a co-twin or sibling in a case report means that neither the history nor the physical examination suggested the presence of congenital cardiovascular disease. Findings on roentgenographic and electrocardiographic examinations, where available, have been included in the case reports.

*Zygosity Determination*

Twin pairs consisting of like-sex co-twins with different blood types, and those having opposite-sex co-twins, were classified as dizygotic.

The pair of conjoined twins was considered monozygotic, as were also those same-sex pairs whose twin partners did not differ in blood types and who strongly resembled each other in general appearance and in the following characteristics: hair color, eye color, shape of external ear, attachment or absence of attachment of the ear lobe to the face, contour of the nose and of the chin in the profile view, and eyebrow shape. Fingerprints were taken of most of the monozygotic twins. In computing the total ridge counts,[59] only the higher count of those fingers with whorl patterns was included. If the prints were not technically satisfactory for obtaining an accurate total ridge count, Brodhage and Wendt's method of evaluating fingerprints[60] was used.

It is extremely difficult to be certain that a pair of twins, other than conjoined twins, is monozygotic. Smith and Penrose[23] have described in detail a method, which we followed, of "evaluating the relative chance that the twin pair is monozygotic." In our computations, we have used the authors' data for the "initial odds" that the pair is dizygotic, and their figures for blood group frequencies (regardless of the ethnic origin of our twins) and for intra-pair differences in fingerprint total ridge counts. In indicated instances, we have incorporated into the mathematical scheme of Smith and Penrose, Wendt's[61] findings on intra-pair differences in fingerprints or Steiner's[62] observations on the number of placentas present in monozygotic and dizygotic twin births. (The "relative chance in favor of a dizygotic pair" is 0.6197 if there is 1 placenta, and 1.931 if there are 2 placentas.) Since we consider that the data on "initial odds" and on blood groups are more reliable than those on fingerprints and placentas, in the case reports we have given one figure for the "relative chance that the twin pair is monozygotic" based on the former data, and have given a second estimate based on the inclusion of data dependent on the fingerprints or the number of placentas.

## Findings

### Twins

Thirty-seven pairs of twins were studied. Two of the 11 monozygotic pairs and 2 of the 26 dizygotic pairs were concordant for the presence of congenital cardiovascular anomalies; all the other pairs were discordant.

*Type of Lesion.* The precise nature of the anatomic lesions of the affected twins has been established in the following 9 instances. The children with patent ductus arteriosus were operated upon and were subsequently free of murmurs. The other diagnoses were made after postmortem examinations.

| Zygosity | Concordance | Case no. | Lesions of affected twins |
|---|---|---|---|
| Monozygotic | Concordant | 36 | One twin had a ventricular septal defect, the other an atrial septal defect. |
| | | 37 | Each twin had a patent ductus arteriosus. |
| | Discordant | 30 | Cor triloculare biatrium. |
| Dizygotic | Discordant | 6 | Dextroposed heart; very small left ventricle; hypoplastic pulmonary artery; atretic pulmonary valve; ventricular septal defect. |
| | | 10 | Ventricular septal defect and pulmonary stenosis. |
| | | 12 | Tetralogy of Fallot. |
| | | 13 | Atrial and ventricular septal defects. |
| | | 18 | Patent ductus arteriosus. |
| | | 24 | Transposition of the great vessels. |

*Noncardiac Anomalies.* Eighteen twins who had congenital cardiovascular anomalies and 7 twins without such lesions had at least 1 other congenital anatomic abnormality or were mentally retarded.

*Birth Weight.* The presence of congenital cardiovascular disease per se did not appear to have any significant or consistent effect on birth weight. The average birth weight of the affected members of the discordant monozygotic twin pairs was 5-4, and of their unaffected co-twins 5-2; the affected twin was the heavier at birth 3 times and the normal twin was the heavier 5 times. Among all discordant pairs of twins, the average birth weight of the affected twins was 5 pounds and of the unaffected co-twins was 5-8; in 10 instances the affected twin was the heavier at birth and in 22, he was the lighter.

### Siblings

The twins were known to have had 74 liveborn, full siblings. Of the 60 whom we examined, 59 had no evidence of congenital cardiovascular disease and 1 had a murmur of undetermined significance. There were 7 living siblings whom we did not examine; their histories did not suggest a cardiovascular lesion. Five siblings had died. Four of them had been immature; postmortem examination of the fifth one showed no cardiovascular lesion. There was no available information about 2 of the siblings.

### Families

*Consanguinity.* There was no consanguinity in any of the families.

*Multiple Births.* Fifty-two multiple births were reported to have occurred among the relatives of 23 twin pairs; they were approximately equally divided between the maternal and paternal lineages. The mothers of 3 of our sets of twins had had other twin pregnancies.

*Congenital Anomalies.* The parents were not aware of any other instances of congenital cardiovascular disease in their families. They reported the presence of the following congenital anomalies among the twins' relatives: syndactyly (1 aunt, 1 greatgrandmother); polydactyly (2 aunts); megacolon (cousin); harelip (uncle); harelip and cleft palate (cousin); and mongolism (distant cousin). A sister and 2 uncles were mentally deficient. A brother had pre-auricular papilloma.

*Familial Disease.* The following relatives of 7 pairs of twins were reported to be diabetic: a maternal aunt (case 35), a paternal grandmother (case 34), and 5 maternal grandmothers (cases 4, 19, 22, 25, 29). The mothers[63] of these 7 pairs of twins had no stillbirths or neonatal losses, and only 1 spontaneous abortion. The average weight of these twins was 5-4, and of their siblings 7-11; the heaviest sibling weighed 9-8.

*Parental Health.* Nothing remarkable was noted with any degree of frequency or regularity in the histories of the health of the parents, other than that 4 mothers had had cholecystectomies. The maternal gynecologic histories were not, in general, unusual. One mother reported that as a baby she herself had received thymic irradiation; another mother had an intravenous pyelogram about a month prior to conception of the twins.

The maternal blood group was known in 23 instances. Ten mothers were group A, 3 were group B, 1 was group AB, and 9 were group O. Twenty-six mothers were Rh positive, and none was known to be Rh negative.

*Obstetrical Histories.* The obstetrical histories of the 36 mothers indicated that 12 of them had a total of 17 spontaneous abortions, 2 had stillborn babies, 1 had an ectopic gestation, and 1 had a hydatidiform mole. They had given birth to 74 living full siblings of the twins. These included 41 male children, 31 females, and 2 children whose sex was not known to us. There were 2 pairs of immature twins who died very shortly after birth. The average birth weight of the sisters of the twins (based on information furnished by the mothers and only sometimes verified) was 7-7, and of the brothers 7-11. There was no consistently long childless interval prior to the conceptions of the twins. The average maternal age at the birth of the twins was 29 years, with a range of 18 to 39 years.

### *Twin Pregnancies*

Twelve mothers reported having had excessive nausea or vomiting during the twin gestations; it occurred during the first trimester in 6 of them, during the latter part of the pregnancy in 2 cases, and throughout pregnancy in 4 instances. Vaginal bleeding was reported in 10 instances. Nine mothers had toxemia.

One mother had rubella in the first month of her pregnancy, 1 had thrombophlebitis in the sixth month, 1 had a renal tract infection in the fourth month, and 1 had pertussis in the fifth month. A cervical polyp was removed from 1 mother 6 weeks after her last menstrual period. Eight mothers appeared to have been under quite severe and protracted nervous tension during the twin pregnancy.

In only 3 instances, were the pregnancies considered normal in retrospect.

The duration of pregnancy was thought to be 38 weeks or less in 22 instances, full-term in 12 cases, and 42 weeks in 2 instances. Thirty-two of the twins weighed less than 5 pounds at birth and 42 weighed 5 pounds or more.

The probable month of conception was calculated from the estimated duration of pregnancy and the date of birth. Conception apparently occurred in November, December, or January in 15 instances; in February, March, or April 8 times; in May, June, or July 7 times; and in August, September, or October 6 times.

The noncardiac aspects of the cases have been summarized in tables 2 and 3. Cases 1 through 14, 25, and 26 represent opposite-sex pairs of twins. The case reports of the monozygotic twin pairs are given in the appendix. Detailed case reports of the dizygotic twins have been deposited with the American Documentation Institute.*

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TABLE 2.—*Family and Gestational Histories: Dizygotic Twin Pairs*

| Family history | | | Maternal history | Twin gestation | | | | | Other known anomalies | |
|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Diabetes | Congenital Anomalies | | Vaginal bleeding | Nervous tension | Toxemia | Miscellaneous | Premature | In twin with cardiovascular anomaly | In noncardiac co-twin |
| Discordant twin pairs | | | | | | | | | | |
| 1. | | + | | | + | | | + | | |
| 2. | | | Pelvic inflammatory disease; sterility | + | | | | + | Cervical ribs | |
| 3. | | (+) | 3 abortions | | | + | | + | | |
| 4. | + | (+) | | + | + | + | | | Retarded physical and skeletal maturation; low-set ears | |
| 5. | | | Many abortions and stillbirths | | | | Probably syphilitic | | | |
| 6. | | | | | + | | | | | |
| 7. | | | | | | | Thrombophlebitis: 6th month | + | Situs inversus; myopia; mental retardation; nonfunctioning kidney; ? Hand-Schuller-Christian; triplet | |
| 8. | | | | | | | Thrombophlebitis: 6th month | + | Situs inversus; myopia; mental retardation; nonfunctioning kidney; ? Hand-Schuller-Christian; triplet | Hernia |
| 9. | | | 2 abortions | | | | | | Rudimentary external ear; facial paralysis; micrognathia; kyphosis; ? mental retardation | |
| 10. | | | | + | | | Rubella: 1st month[64] | + | Bilateral cataracts | Bilateral cataracts |
| 11. | | | | + | | | Pertussis: 5th month | | Congenital deafness; marked freckling of skin; very light-colored irides; external ears protrude | |
| 12. | | | 1 abortion; a Montgomery-Simpson suspension; salpingo-oophorectomy | + | | | Cervical polyp removed: 6 weeks | + | | |
| 13. | | | Sterility | | | | | | | |
| 14. | | | | | | | Uterine inertia and hemorrhage during delivery | | | |
| 15. | | | | | | | | | | |

*(Continued on next page)*

TABLE 2.—*Family and Gestational Histories: Dizygotic Twin Pairs (Continued)*

| Family history | | | Maternal history | Twin gestation | | | | | Other known anomalies | |
|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Diabetes | Congenital Anomalies | | Vaginal bleeding | Nervous tension | Toxemia | Miscellaneous | Premature | In twin with cardiovascular anomaly | In noncardiac co-twin |
| 16. | | (+) | | | + | + | Partial placenta previa | | | |
| 17. | | (+) | | | + | + | | + | Severely retarded; impaired vision; turret-skull; thick tongue | |
| 18. | | | 1 abortion | | | | Vaginal discharge: first 4 months | + | | Mental retardation |
| 19. | + | | | + | | + | | + | | |
| 20. | | | 1 abortion; sterility | | + | | | | | |
| 21. | | | | | | | Moniliasis at 4½ months | | | |
| 22. | + | | 1 abortion | + | | | | + | | |
| 23. | | | Rheumatic | | | + | | + | Umbilical hernia | |
| 24. | | (+) | Hydatid mole; cholecystectomy | | | | Severe vomiting: 1st trimester | | Hemangioma of lung | |
| Concordant twin pairs | | | | | | | | | | |
| 25. | + | | Cholecystectomy | + | | | | | A. —<br>B. Mental retardation; hypospadias; cryptorchidism; short 5th fingers; protruding ears | |
| 26. | | | 3 abortions; sterility | | | | Severe varicose veins | + | A. Hare-lip; cleft palate; colobomas; microphthalmos; macrocephaly; abnormal vertebrae<br>B. — | |

*Note*: + in the congenital anomalies column indicates that one of the twins' siblings had an anomaly; (+) that some other relative had an anomaly.

## DISCUSSION

It is reasonable to suppose that there are various mechanisms causing human congenital cardiovascular lesions. Like older individuals, the newborn baby doubtless is as he is because of the interaction of his genetic endowment and his previous environment. Yet we postulate that either a hereditary or an environmental factor was the more influential (or at times, possibly, the sole) mechanism in the production of an anomaly in any particular baby. An indication of the relative etiologic importance of the genetic and environmental factors may be gained if we can explain the discordance of the twin pairs.

Although discordance of dizygotic twin pairs is certainly compatible with the idea of a primarily genetic etiologic mechanism, the discordant monozygotic pairs (consisting of individuals with similar genetic endowment) militate against this postulate.

An environmental teratologic factor could affect a fetus in one of 2 general ways—via the maternal circulation, or locally at a site very close to the ovofetus. In the former

TABLE 3.—*Family and Gestational Histories: Monozygotic Twin Pairs*

| Family history | | | Maternal history | Twin gestation | | | | | Other known anomalies | |
|---|---|---|---|---|---|---|---|---|---|---|
| Case No. | Diabetes | Congenital Anomalies | | Vaginal bleeding | Nervous tension | Toxemia | Miscellaneous | Premature | In twin with cardiovascular anomaly | In noncardiac co-twin |
| Discordant twin pairs | | | | | | | | | | |
| 27. | | (+) | Thymic irradiation as baby; menstrual irregularities; 1 abortion | | | + | | | Syndactyly | Syndactyly; abnormal incisor |
| 28. | | | | | | + | | + | Mental retardation | Mental retardation |
| 29. | + | | Cholecystectomy | | | + | | + | | Strabismus |
| 30. | | | | | | | Severe vomiting: 1st trimester | + | Conjoined twin; Situs inversus | Scoliosis |
| 31. | | | 1 abortion during prior marriage | | + | | Labor-like abdominal pains: 2nd month | + | Mental retardation | Mental retardation |
| 32. | | | | | | | Urinary tract infections: 4 and 7½ months | + | | |
| 33. | | | 1 abortion | | | | | + | | |
| 34. | + | | Menstrual irregularities; infantile uterus; I.V.P. 2½ weeks before last menstrual period | + | | | | + | | |
| 35. | + | | Cholecystectomy | | | | | | Ptotic eyelid | |
| Concordant twin pairs | | | | | | | | | | |
| 36. | | + | 1 stillbirth; 2 cesarean sections | | | | | + | A. Mongol · B. Mongol | |
| 37. | | | Ectopic gestation and salpingectomy; 2 abortions during prior marriage | + | + | | | + | | |

Notation same as table 1.

event, the fetus could be damaged (1) by an excessively high concentration in the maternal blood of a substance, such as a hormone or nutrient, which is normally present; (2) by maternal deficiency of some substance, such as a hormone, or a nutrient, or an enzyme, or oxygen; or (3) by the abnormal presence of an injurious chemical or infectious agent.

The discordant monozygotic twin pairs make it very difficult to accept the concept of an etiologic factor transported by the maternal circulation, since genetically similar embryos would be expected to react in a similar fashion to the same environmental stimulus. Although discordance of dizygotic pairs would be a somewhat surprising finding were the teratologic agent blood-borne, there could be at least 2 explanations for such discordance. Either the co-twins could differ genetically in their susceptibility to the environmental factor, or the co-twins could have reached slightly different stages of development at the time of the insult, with only 1 twin at the critically susceptible period for the production of the anomaly.

A more satisfactory explanation of the discordance of the monozygotic twin pairs

appears to us to be that of an environmental factor acting in close proximity to the zygote, embryo, or fetus, so localized that it can affect 1 twin and leave his co-twin unscathed. The insult may occur in the uterus, for instance, in one of the following ways described by Javert:[74] "When one recalls the physiologic anemia which characterizes the early development of the ovofetus, it does not take much more than a simple twist of the cord, or a small area of decidual hemorrhage, or avascularity of the villi, or a faulty implantation, to compromise normal oxygenation and nourishment of the ovofetus, and its subsequent faulty development." Or the damage may be inflicted in or by the oviduct. Or the responsible agent may be in the cytoplasm of the ovum. If such locally operative factors can, indeed, constitute a type of teratologic mechanism, the problems of delineating their nature and of determining what produces them are posed.


## Summary

Twenty-six pairs of dizygotic twins and 11 pairs of monozygotic twins were studied. In 2 of the former and 2 of the latter, both twin partners had congenital cardiovascular anomalies. Only 1 member of each of the remaining pairs had a congenital cardiovascular lesion. The problem of the etiology of the malformations is discussed in the light of these findings.



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## Appendix

In the following case reports, each twin is designated by 3 letters. The first indicates whether he did (C) or did not (N) have congenital cardiovascular disease; the second indicates whether the individual was male (M) or female (F); the third refers to his having been born first (A) or second (B).

### *Monozygotic Pairs Discordant for Cardiovascular Anomalies*

*Case 27.* The paternal greatgrandmother and a daughter of the maternal grandmother's sister were thought to have syndactyly. When the twins' mother was a baby, her thymus was irradiated. She had had menstrual irregularities from the time she was 18 years old until after the birth of the twins. Her first pregnancy ended in a missed abortion at about 4½ months. A son was born the next year, following which she had intermittent pyrexia of unknown etiology for 2 to 3 months. About 3½ years later, she was considered well enough to have more children, and promptly conceived.

The mother was given some type of injections to preserve the twin pregnancy. Albuminuria and ankle edema were present during the last week; on the day of delivery and on the following day, her blood pressure varied between 135-170/90-100. The duration of pregnancy was not definitely known, but it was thought probably to have been full-term. The twins were born when their mother was 24 and their father 25 years old. NMA weighed 5-13 at birth, and CMB 4-13.

A systolic murmur was noted when CMB was 1 week old. He had noisy breathing and occasional coughing and choking spells as a baby; these symptoms gradually subsided. He always weighed less than his co-twin. His mother felt that he was asymptomatic and that he tired a little less easily than, and was physically stronger than his normal co-twin.

At 6½ years of age, the patient weighed 48 pounds. The proximal phalanges of his second and third toes were fused bilaterally. There was mild bilateral parasternal prominence. He had a grade III, harsh, systolic murmur, loudest at the lower left sternal border; the murmur was transmitted laterally and up the left sternal border. An esophagram at age 3 years and a chest x-ray and an electrocardiogram at 6 years of age were within normal limits. The only finding of possible significance was an R′ wave, 1 mm. in amplitude, in lead $V_1$; the intrinsicoid deflection in this lead was 0.05 second. Cardiac catheterization, performed when CMB was 6 years old, was suggestive, although not definitely diagnostic, of an interventricular septal defect, the presumptive clinical diagnosis.

The co-twin weighed 10 pounds more than and was 2½ inches taller than the patient. He had the same abnormality of the toes as did CMB. A right lateral incisor, a temporary tooth, was about twice as wide as normal. The non-twin brother did not have syndactyly.

Zygosity: The twins resembled each other very much. The blood typing of the family was as follows:

| | Blood group | Rh$_0$ | rh′ | rh′′ | hr′ | Kell | Duffy | MN |
|---|---|---|---|---|---|---|---|---|
| Twins | O | Pos. | Pos. | Neg. | Neg. | Neg. | Neg. | MN |
| Mother | O | Pos. | Pos. | Neg. | Neg. | Neg. | Neg. | MN |
| Father | O | Pos. | Pos. | Neg. | Pos. | Pos. | Pos. | M |
| Brother | O | Pos. | Pos. | Neg. | Pos. | Pos. | Pos. | MN |

The difference in the fingerprint total ridge counts was 1. The relative chance that this pair of twins was monozygotic was 0.9322; it was 0.9836 if the fingerprint data were included.

*Case 28.* The paternal grandmother and a paternal aunt had twins. The mother's blood group was A, type Rh positive. The twins were born during the first year of the parents' marriage; the mother was 19 and the father 26 years old at the time. Another daughter was born a year later, and a fourth one 4 years after that.

The mother reported that she had excessive nausea and vomiting during the last few months of her pregnancy. Her blood pressure was elevated from the beginning of the second trimester; the highest pressure, 180/100, was noted 2 days before the twins were born, at which time she also had 3+ edema of the extremities. The duration of pregnancy was 7 months. NFA weighed 4-10 and the patient weighed 4-6 at birth. There was a single placenta and 2 umbilical cords.

The presence of a murmur was recorded when CFB was 5 years old. She was less active than her twin, but it was difficult to determine whether this was the result of diminished exercise tolerance or of greater mental retardation. Her I.Q. was 38; NFA's was 52. CFB was always the smaller twin. When 7 years old, she weighed 44 pounds and was 45 inches tall; her co-twin weighed 55 pounds and was 50 inches tall.

At 9 years of age, CFB weighed 54 pounds and was 50 inches tall. The point of maximal cardiac impulse was palpable in the sixth intercostal space, medial to the midclavicular line. The second sound at the pulmonary area was of normal intensity and was split. There was a grade IV, harsh, systolic murmur, maximally intense at the left sternal border in the second intercostal space, transmitted

down the left sternal border, and audible posteriorly. There was also a short, grade III, diastolic murmur along the left sternal border. Moderately marked transverse enlargement of the heart, with enlargement of both the right and left ventricles, was noted on fluoroscopic examination. The electrocardiogram was suggestive of right ventricular hypertrophy. It was thought that the child had more than one anatomic lesion, but the diagnosis was not clear.

NFA weighed 69 pounds and was 56 inches tall. Physical, electrocardiographic (including precordial leads), and fluoroscopic examinations showed no abnormalities. (Neither twin had any findings in the facies or hands suggestive of mongolism.)

Zygosity: The twins were Negro children who resembled each other, but could be differentiated because of their difference in size. Both twins were group $A_2$, type MNss, $Rh_1rh$, Duffy negative, Kell negative, P negative. All the fingerprints of both girls were ulnar loops. The difference in total ridge counts was 6. The relative chance that they were monozygotic was 0.9533: it was 0.9931 if the single placenta and fingerprints were considered.

*Case 29.* The maternal grandfather's brother's daughter and the paternal aunt had twins. A daughter of the same paternal aunt had a pair of opposite-sex twins. The maternal grandmother died in diabetic coma. The twins' mother had a cholecystectomy when she was 52 years old, and their father had a similar operation when he was 54 years old. At about the same time, he was discovered to have polycythemia.

Two and a half years after the parents were married, they had a daughter. A son was born 5 years after that, and another one 3 years later. Four years subsequently, after a 5-months' gestation, twin sons were born and died almost immediately. CFB and NFA were born 2 years later; their mother was 36 years old then and their father 38.

The mother was hospitalized prior to the birth of the twins for treatment of toxemia. Her average blood pressure was about 150/90 mm. Hg, she had 3+ albuminuria, and gained 12½ pounds during the final month of pregnancy. The twins were born after a 36-week gestation; NFA weighed 4-2 and CFB weighed 6-5. There was a single placenta.

At 4 months of age, CFB developed cyanosis which lasted for a few months. She always tired somewhat more easily than NFA; she teethed and walked a little later than her co-twin, and had to study more intensively than her sister in order to achieve the same marks in school. The mother reported that CFB had frequent upper respiratory infections, and whooping cough, scarlet fever and measles which her normal twin did not contract. However, CFB always weighed more than NFA and her menarche occurred at 12 years of age, 6 months prior to NFA's.

At 17½ years of age, CFB weighed 110 pounds and was 5 feet 2 inches tall. She was right-handed. She had a grade IV, harsh, systolic murmur, which was maximally intense at the left sternal border in the fifth intercostal space, and was widely transmitted. The fluoroscopic and electrocardiographic (including precordial leads) findings were within normal limits. The girl was thought to have a ventricular septal defect.

Her co-twin weighed 98 pounds and was 5 feet 2 inches tall. She was left-handed. Both she and the older brother were said to have had strabismus which had been surgically corrected.

Zygosity: Both girls were blood group A, type $Rh_1Rh_1$, Mss, Duffy positive, P negative, Kell negative. There were 3 fingerprint pattern differences; the difference between their fingerprint counts (by the method of Brodhage and Wendt) was 2. The relative chance that this pair of twins was monozygotic was 0.9750; it was 0.9956 if the data for the placenta and fingerprints were included.

*Case 30.* These conjoined twins were the products of their mother's first pregnancy, and were conceived a few weeks after her marriage. The father was 23 years old when they were born and the mother was 25. The parents were Negroes. Another daughter was born 1 year after the twins.

The mother had excessive vomiting during the first trimester, with a weight loss of 15 pounds during the early part of the pregnancy. When 3½ months pregnant, she had 9.2 Gm. Hb per 100 ml. and 3,600,000 red blood cells per $mm.^3$ The twins were born after a 36-week gestation. CFA weighed about 3-10. The conjoined co-twin was stillborn and weighed about 2-2. There was a single, large placenta and a single umbilical cord. The twins were surgically separated soon after birth. CFA died at 8 hours of age.

The twins were fused from below the xiphoid to the pubis; there was a cartilaginous bridge in the xiphoid region. They had one large liver, a single biliary tract, and a large, bifid gallbladder. The gastrointestinal tracts were continuous at the upper jejunal level. Each baby had her individual stomach, large intestine, and genitourinary tract. CFA's spleen was on the right side.

CFA had a cor triloculare. The tricuspid valve and the right ventricle were absent; the pulmonary artery was atrophic. The ductus arteriosus and the foramen ovale were patent. The heart weighed 30 Gm. The stillborn baby's heart weighed 4 Gm., and appeared anatomically normal. Her ductus

arteriosus and foramen ovale were also patent; these findings were considered "physiological." She had marked bilateral pulmonary atelectasis and severe left dorsolumbar scoliosis. Their younger sister was examined when she was 21 months old.

Of interest in connection with this case, are other conjoined twins discordant for congenital heart disease[65–67] and a pair who were probably concordant for it.[68]

*Case 31.* The family history was incomplete. During the mother's first marriage, she had seven pregnancies, productive of 5 full-term babies, one premature baby who weighed 3½ pounds at birth, and one spontaneous abortion of a 6-month fetus. The son of a half-sibling of the twins had a club foot. The only pregnancy during the mother's second marriage was that productive of the twins who were born 9 years after their youngest half-sibling. Both parents were 36 years old at the time of the twins' birth.

The mother had labor-like abdominal pains during the second month of the twin gestation; she was treated with stilbestrol. The duration of the pregnancy was 8 months. Both umbilical cords prolapsed late in labor. The onset of respiration was delayed in both twins, and they required tracheal aspiration. NMA weighed 5-3 and the patient weighed 4-13 at birth. There was one placenta.

CMB was noted to have a murmur when he was 10 months old. He seemed to tire a little more easily than his co-twin, and reached his landmarks slightly later than did NMA. His I.Q. was 49 and his co-twin's was 47.

At 9 years of age, CMB weighed 49 pounds and was 49 inches tall. He had a grade III to IV, harsh, systolic murmur which was loudest at the left sternal border in the fourth intercostal space and was transmitted laterally and up the left sternal border. The second sound at the pulmonary area was accentuated and split. An electrocardiogram, which included precordial leads, was recorded when he was 7½ years old, and was normal. Roentgenographic examination at that time showed increased bronchovascular markings and questionable lifting of the apex. He was thought to have a ventricular septal defect.

The co-twin weighed 53 pounds and was 50 inches tall. Physical, electrocardiographic (including precordial leads), and fluoroscopic examinations at 9 years of age revealed no cardiovascular abnormalities. He had a Simian crease on the right hand; CMB had one on the left hand. Neither twin had any facial findings suggestive of mongolism.

Zygosity: The color of the normal twin's skin was a little darker than that of the affected twin; they were Negroes. Both twins were group O, type $Rh_0$, Mss, P positive, Duffy negative, Kell negative. The difference in their fingerprint total ridge counts was 3. The relative chance that they were monozygotic was 0.9417; it was 0.9913 if the placenta and fingerprints were considered too.

*Case 32.* The mother's paternal grandmother had twins. The father developed an inguinal hernia at 12 years of age. The twins had 2 brothers, the first of whom was born 2 years after the parents' marriage. The twins were born 2½ years later; both parents were then 25 years old. The youngest child was born 16 months after the twins.

The mother's last menstrual period prior to the twin pregnancy began on April 17. On August 14, she developed a urinary tract infection for which she was treated with gantrisin and penicillin. Her hemoglobin at the time was 9.4 Gm. per 100 ml. A month before delivery, the mother probably had a recurrence of the infection, and was treated with gantrisin and aureomycin. At this time, her hemoglobin was 8.4 Gm. per 100 ml. and her red blood count was 2,790,000 per $mm.^3$ The twins were born on December 28. NMA weighed 5-14 and CMB 6-0. There were two completely separate placentas.

The 2 babies developed adequately and in a similar fashion for approximately 3 months. Then CMB's appetite diminished and he failed to gain well. He developed respiratory difficulties (frequent coughing, wheezing, and labored breathing), became seriously ill, and was hospitalized on 4 occasions during the first 2 years of his life. Marked enlargement of his heart, especially of the left ventricle, was noted when he was 4 months old. The baby was treated with digitalis until the age of 4½ years. At 1 year, he weighed 17 pounds and his co-twin weighed 23 pounds. CMB began to improve at about 2½ years of age, and within half a year, he was the equal of his co-twin in weight, height, and physical activity, according to his mother.

There were no significant murmurs at the beginning of his illness, but by the time he was 4 years old, an organic-sounding systolic murmur was present, and when he was 6 years old, a diastolic murmur was also noted. Angiocardiography (at 6½ years of age) revealed a tremendous left ventricle with thick walls; there was minimal increase in the size of the left atrium. There was electrocardiographic evidence of left ventricular hypertrophy.

At 7 years of age, both twins weighed 52 pounds and were 4 feet tall. CMB had a slight precordial bulge. The point of maximal impulse was palpable at the midclavicular line in the sixth intercostal space. There was a grade III,

harsh, systolic murmur, maximally intense at the apex, and transmitted up the left sternal border and to the axilla. There was an inconstant, grade II, apical diastolic "thud." The nature of the cardiac disease was not definitely established, but it was considered most likely that the boy had "cured" fibroelastosis.

Zygosity: The boys resembled each other very, very much. Both were group O, type $Rh_1Rh_1$, Mss, P positive, Duffy positive, Kell positive. The difference between their fingerprint total ridge counts was 13. The relative chance that they were monozygotic was 0.9420; it was 0.9590 if the placentas and fingerprints were taken into consideration.

Ullrich[9] reported endocardial fibrosis in the 2 monozygotic brothers of a set of triplets, and Greaves et al.[33] described endocardial fibroelastosis in both of a pair of "identical" twins.

*Case 33.* The family history was incomplete and unreliable. The mother's blood was group O, type Rh positive. The twins had a brother of 20 years who was not examined by us, but who was considered free of heart disease on 2 Service examinations, and a 16-year-old brother. The mother had a spontaneous abortion of the products of a 3 months' gestation about a year after the birth of her first child.

The twins were born 7 years after their younger brother, when the mother was 33 and the father 38 years old. The mother was bothered throughout the twin pregnancy by "spitting up water." The twins were born 3 weeks prematurely. CMA weighed 4-12 and his co-twin 5-2. There was 1 placenta; the presence of 1 chorion and 2 amnions was reported on the basis of gross examination.

A murmur was detected when CMA was 3 years old. He was slightly more dyspneic than the average child after climbing 3 flights of stairs, but otherwise asymptomatic. His mother considered him mentally more alert and physically stronger and more pugnacious than NMB.

At 8 years of age, CMA, a Negro boy, weighed 57 pounds and was 50½ inches tall. He had a grade II, blowing, systolic murmur, loudest at the left sternal border in the third intercostal space and transmitted locally. Fluoroscopic examination revealed a full pulmonary artery segment and mild left ventricular enlargement. There was an RSR′ pattern in precordial leads $V_1$ and $V_2$ of the electrocardiogram; the intrinsicoid deflection was 0.05 second in $V_1$. The presumptive clinical diagnosis was an atrial septal defect.

The co-twin was the same height as CMA and weighed 9 pounds more. Physical, electrocardiographic (including precordial leads), and fluoroscopic examinations showed no cardiovascular abnormality. The 16-year-old brother had a soft, blowing, systolic murmur at the left sternal border in the second and third intercostal spaces; it was not transmitted and was audible in the supine, but not in the erect position. The clinical impression was that the murmur was innocent; however, since electrocardiographic and fluoroscopic examinations could not be made, the boy was considered to have an undiagnosed manifestation.

Zygosity: The twins looked very much alike, except that the face of the heavier one was rounder than his brother's and that there was some difference in the shapes of their eyebrows. The presence of a single chorion indicated that the twins were monozygotic. In case the clinical impression of a single chorion may have been in error, the following information is included. Both twins were group O, type $Rh_2rh$, Nss, P positive, Duffy negative, Kell negative, Kidd negative. The difference between their fingerprint total ridge counts was 9. The relative chance that they were monozygotic was 0.9556, or 0.9926 if the single placenta and the fingerprints were taken into consideration.

*Case 34.* The paternal grandfather's sister and the paternal grandmother's cousin's daughter had twins. The paternal grandmother had diabetes. Prior to her marriage, the mother had severe dysmenorrhea and menstruated at 4- to 6-week intervals. She was told that she had an infantile uterus. At about the time of her marriage her basal metabolic rate was —18. The twins were the parents' first children and were born when the mother was 25 and the father 35 years old. Two years later they had a son, born after a 41-week gestation. A second son was born 1½ years after the first.

Seven weeks after her marriage, the mother had acute cystitis; *Bacillus pyocyaneus* was cultured from the urine. She was treated with aureomycin. Excretory urography was performed and was normal. Her last menstrual period prior to the twin gestation began 18 days after the urography. The mother vomited excessively during the first 2 or 3 weeks of the pregnancy, and had vaginal staining for 2 days at the time of her fourth and fifth missed menstrual periods. The twins were born 5 weeks prematurely; CFA weighed 5-5 and NFB weighed 4-2.

CFA was noted to have a murmur at birth. She was asymptomatic and the twins' growth and development were very similar. The mother considered the affected twin to be physically more

active than her sister. CFA was 4 pounds heavier than her sister until they were 6 years old.

At 7 years of age, both twins weighed 50 pounds and were 43½ inches tall. CFA had several black nevi about 2 mm. in diameter on the anterior and posterior chest. She had a systolic thrill and a grade VI, coarse, systolic murmur at the left sternal border in the third intercostal space; the murmur was widely transmitted and was audible posteriorly. The second sound at the pulmonary area was inaudible. Cardiac catheterization demonstrated the presence of pulmonary stenosis; the pressure in the right ventricle was 144/10. The catheter could be passed from the right to the left atrium, probably through a patent foramen ovale, since there was no significant increase in the oxygen content of the blood at the atrial level. Valvulotomy and dilatation of the stenotic pulmonary valve were performed when the child was 8 years old.

Zygosity: There was a striking resemblance between the twins. Both were blood group A, type $Rh_1Rh_2$, Nss, P negative, Kell negative, Duffy negative. The difference between their fingerprints as evaluated by the method of Brodhage and Wendt was 3. The relative chance that they were monozygotic was 0.9578; it was 0.9783 if the fingerprint data were considered also.

*Case 35.* The father's brother's son had a pair of opposite-sex twins. The mother's sister had asthma, diabetes, and severely impaired vision and hearing. The mother became hard-of-hearing when she was about 47 years old, and had a cholecystectomy at about the same age. A year after their marriage, the parents had a daughter. The twins were born 4 years later, after a full-term, uncomplicated pregnancy, according to the history obtained from the mother. (No medical records were available and the serology was not known.) The mother recalled that she ate no meat during the pregnancy, and that she ate very many pumpkin seeds. At birth, CMB weighed 5-7 and NMA weighed 6-3. There was one "afterbirth."

Ptosis of CMB's left upper eyelid was present from birth. During the first 3 years of his life, he, unlike his co-twin, had a poor appetite and very many upper respiratory infections.

Coaretation of the aorta was discovered when CMB was 16 years old, and was confirmed the following year on angiography. Between the ages of 16 and 23 years, CMB had progressive increase in blood pressure, some dizziness, some blurring of vision, and mild girdling pains of the lower rib cage. Roentgenographic evidence of notching of the ribs was present when he was 20 years old. Surgery was performed when he was 22½ years old. The narrowed area of the aorta was located at the level of the ligamentum arteriosum, distal to the origin of the left subclavian artery. The outer diameter of the coarcted region was 11 mm. and the inner diameter was 3 mm. There was post-stenotic dilatation of the aorta; just distal to the coaretation the outer diameter of the aorta was 25 mm., whereas above the coarctation it was 16 mm. A segment of the aorta 2 cm. in length was removed and an end-to-end anastomosis was performed.

At 27 years of age, CMB was 5 feet 4 inches tall and weighed 145 pounds. Partial ptosis of the left upper eyelid was present. His blood pressure was 128/68 and the pulsation of the dorsalis pedis artery was palpable. A grade III, harsh, systolic murmur was present. It was loudest at the left sternal border in the second intercostal space when CMB was in the erect position, and at the lower left sternal border when he lay down; the murmur was widely transmitted in both positions.

NMA was the same height as his twin, and weighed about 12 pounds less. He had neither ptosis nor clinical evidence of cardiovascular disease. His blood pressure was 118/78.

Zygosity: We were not able to see the men together. Through high school age, the twins were often confused; their mother has considered them "identical." Their hair color, eye color, and ear lobes were similar. Both were group O, type $Rh_1Rh_2$, M, S positive, P positive, Duffy positive, Kell negative. The difference in their fingerprint total ridge counts was 15. The relative chance that they were monozygotic was 0.8979; it was 0.9752 if the placental and fingerprint data were taken into consideration also.

### *Monozygotic Pairs Concordant for Cardiovascular Anomalies*

*Case 36.* The mother's first pregnancy was productive of a stillborn, macerated baby girl who weighed 9-14 and was born 2 years after the parents' marriage. No fetal heart sounds had been heard for 2 days prior to her birth. At the time of delivery, the mother had an upper respiratory infection; her husband had had a viral infection shortly before that. At postmortem examination of the stillborn baby, both the foramen ovale and the ductus arteriosus were observed to be patent; these findings were not considered pathologic. There were multiple, small, white, infarcted areas in the placenta.

Since the mother's pelvis had a contracted outlet, her next baby, born a year later, was delivered by elective cesarean section performed after 38 weeks' gestation. The boy weighed 7-8;

he had a pre-auricular papilloma. There were extensive calcified deposits in the placenta. Two years later, another son was delivered by elective cesarean section a week before term; he weighed 8-10. Neither of these 2 boys was examined by us; their pediatrician reported them free of congenital heart disease at 7 and 5 years of age.

The twins were born a year and a half after their younger brother. The father was then 42 years old, and the mother at least 38 years old. The pregnancy lasted 38 weeks. A cesarean section was performed after the mother went into labor. There was a single placenta. The first-delivered twin weighed 4-11 and the second 5-8. Both babies were considered mongoloid from birth.

CMA had a murmur from birth, and died at 2½ months of age, weighing 9 pounds. He had blue eyes and brown hair. Postmortem examination of the heart showed that there was a 4 by 3 cm. defect in the ventricular septum "about 3 mm. below the aortic ring and underneath the anterior cusp." The foramen ovale was closed.

A systolic murmur was intermittently heard in the second twin. He died of bronchopneumonia at 5 months of age; he weighed 8-5 at the time. He, too, had blue eyes and brown hair. At postmortem examination, an open foramen ovale was noted; as this term is used by the pathologist who examined the heart, it indicated that there was an anatomic defect of at least 1/3 of the area of the atrial septum.

Zygosity: Both twins were group A, type Rh positive. Allen and Baroff[69] considered the maximal concordance rate for mongolism among dizygotic twins to be 2.7 per cent. The probability that the twins were monozygotic, calculated from this figure as well as those based on our knowledge of the "initial odds," blood types, and placenta was 0.9887.

The following reports of twin pairs concordant for mongolism are of interest in connection with this case. Both members of the pair described by Rosanoff and Handy[70] were considered to have congenital heart disease. It is difficult to judge whether the "systolic murmur" heard in both co-twins reported by Lund[71] was caused by congenital heart disease. A pair apparently discordant for congenital cardiac disease was described by Jervis;[72] the question of their zygosity was later discussed by Allen and Baroff.[69] Young[73] reported a pair of twins, one of whom showed no evidence of heart disease during the first seven weeks of life, although his co-twin was definitely affected.

*Case 37.* The mother was receiving psychiatric therapy on an ambulatory basis at the time of our interview. She gave a history of having been married twice. During her first marriage, and beginning at 16 years of age, she had 4 pregnancies, productive of 2 full-term children (one of whom was examined by us), an abortion of twins, and an abortion of a single fetus. The mother was pregnant 6 times during her second marriage. A daughter was born 15 months before the twins. Nine months before their birth, the mother had a salpingectomy for a ruptured ectopic pregnancy. The twins were born when the mother was 23 years old. A girl was born 3 years after them; during this pregnancy, the mother took an overdose of sleeping tablets. A boy was born the following year, and another one 14 months later. During the final pregnancy, the mother voluntarily entered a mental hospital for 10 days. She was sterilized after the birth of this, her eighth living child.

During the twin gestation, the mother "spotted" for 4 days in the second month, and again in the fourth month. The twins were born after a 33-week gestation; CFA weighed 3-15 and CFB weighed 3-11. There was a single, large placenta.

Both children underwent cardiovascular surgery when they were 1½ years old. Each had a patent ductus arteriosus, which was about 5 mm. in diameter. The attachment of the pericardium to the pulmonary artery and the ductus arteriosus was firmer and more extensive than usual. CFA's ductus was ligated, and her sister's was divided.

The twins had no clinical evidence of cardiovascular disease when examined at 6 years of age. Each weighed 42 pounds. CFA was 42 inches tall and CFB was 44½ inches tall. CFA had a very small umbilical hernia not present in CFB.

Zygosity: The little girls resembled each other very, very much. Both were group O, type $Rh_0$, MN, S positive, P positive. The difference in their fingerprint total ridge counts was 10. The relative chance that they were monozygotic was 0.8874; it was 0.9823 if the data on the placenta and the fingerprints were included.

Mc Aleese,[36] Holman et al.,[37] and Starer[38] have also described "identical" twin pairs concordant for patent ductus arteriosus. However, several probably monozygotic twin pairs discordant for a patent ductus have also been reported.[14, 22, 38, 41]

# Chronic Cor Pulmonale in Delhi

## A Study of 127 Cases

*By* S. Padmavati, F.R.C.P., M.R.C.P., and S. N. Pathak, M.R.C.P., D.C.H.

The incidence of chronic cor pulmonale in Indian states, including Delhi, is the highest reported in nonindustrial populations. The patients presented as acute severe congestive heart failure and at younger ages than those reported. In many cases there was only a short history of respiratory symptoms. Following the first attack of failure, repeated attacks were the rule and death ensued within 2 years. A study is presented of 127 patients of this type in Delhi with clinical and laboratory data and autopsy data of 4 cases. The probable causes of these peculiar features are discussed.

THE high incidence of chronic cor pulmonale in Delhi prompted this study with a view to elucidating its etiology. Although statistics regarding heart disease from the various states of India are meager, the few available indicate that the incidence of this condition in Delhi is one of the highest. In statistics of routine hospital admissions Jaipur is the only state from which a high incidence of pneumoconiosis has been reported.[1] A comparison for different parts of India of the incidence of cor pulmonale shown as percentage of all cardiac cases suggests that it is much more prevalent in the northern part of India than in the west (table 1).

By contrast, figures from most western countries are low except when they are from industrial areas (table 2). While the incidence as reported from hospital statistics is nowhere near the figures from India, those from industrial areas show an incidence as high as or higher than those for Indian states. Thus Gooding,[11] in reporting on 227 postmortem examinations on miners certified as having pneumoconiosis, found no less than 37 per cent dying of cardiac failure. Flint[8] in a recent study of 300 cases of congestive heart failure at Sheffield in iron and steel workers, reported an incidence of cor pulmonale of 40 per cent among men and 8.5 per cent among women with a total incidence of 25 per cent among all types of heart disease. Other workers[12–15] reported a high incidence among coal miners. There is perhaps an underestimate of the true incidence of cor pulmonale, owing probably to the masking of the cardiac signs by the physical signs of the underlying lung disease. Thus White and Brenner,[16] and Parkinson and Hoyle[17] found a low incidence of cardiac failure from emphysema, bronchial asthma, and pulmonary tuberculosis. McMichael,[18] however, was of the opinion that chronic cor pulmonale was much more common than statistical evidence would indicate. This study from Delhi is of interest because of the high incidence in a nonindustrial population.

In Delhi, out of 132,794 cases admitted to the 2 large hospitals (Lady Hardinge and Irwin Hospitals), cor pulmonale accounted for 392 cases between 1950 and 1955 (0.3 per cent). Out of 2,360 cardiac cases admitted to these hospitals in the same period cor pulmonale accounted for 392 cases, giving an incidence of 16.6 per cent. The proportion of males to females was 211:181 (1.2:1.0).

The present detailed study relates only to patients from the Lady Hardinge Hospital, about whom it was possible to get definite data and adequate records. There were 123 women and 4 men in this series. In the Medical Unit of the Lady Hardinge Hospital, of 7,113 patients admitted during the 5-year period (1953 to 1957), there were 122 cases

From the Department of Medicine, Lady Hardinge Medical College, New Delhi, India.

TABLE 1.—*Incidence of Cor Pulmonale in Indian States*

| | Delhi[2] | Bombay[3] | Amritsar[4] | Jaipur[1] | Lucknow[5] |
|---|---|---|---|---|---|
| Cardiac cases | 2360 | 1860 | 500 | 342 | 1000 |
| Cor pulmonale cases | 392 | 186 | 54 | 108 | 185 |
| Percentage | 16.6 | 10.0 | 10.8 | 31.6 | 18.5 |

TABLE 2.—*Cor Pulmonale in Countries Outside India*

| | Wood[6] (1950) | Philippines[7] (1955) | Sheffield[8] (1954) | New England[9] (1953) | Texas[10] (1953) |
|---|---|---|---|---|---|
| Cardiac cases | 10,000 | 4304 | 300 | 3000 | 1000 |
| Cor pulmonale percentage | 0.45 | 4.2 | 25.0 | 1.1 | 0.6 |

TABLE 3.—*Age Incidence of Cor Pulmonale*

| Age in years | Below 10 | 10—19 | 20—29 | 30—39 | 40—49 | 50—59 | 60 and above |
|---|---|---|---|---|---|---|---|
| Number of patients | 1 | 2 | 9 | 29 | 43 | 29 | 14 |
| Percentage | 0.8 | 1.6 | 7.1 | 22.8 | 33.8 | 22.8 | 11.1 |

TABLE 4.—*Underlying Pulmonary Disease*

| Disease | No. of patients | Percentage |
|---|---|---|
| Chronic bronchitis | 76 | 59.8 |
| Bronchial asthma | 17 | 13.4 |
| Bronchiectasis | 22 | 17.3 |
| Pulmonary tuberculosis | 7 | 5.5 |
| Chest deformity | 3 | 2.4 |
| Primary pulmonary hypertension | 2 | 1.6 |

of cor pulmonale, accounting for 1.7 per cent of all medical admissions. Out of 706 cardiac cases admitted during the same period, cor pulmonale accounted for 17.3 per cent of cases. By contrast, in a 5-year survey (1951 to 1955), rheumatic heart disease accounted for 39.1 per cent and degenerative heart disease for 11.3 per cent.[2]

A large number of these cases of cor pulmonale was not seen in the out-patient department, as on their very first attendance the patients were ill enough to be admitted directly into the wards, without going through the cardiac clinic. Of 1,069 cases registered from 1952 to 1957 there were only 51 cases of cor pumonale (4.8 per cent), according to the out-patient cardiac clinic records—an erroneously low figure.

In an industrial survey of 500 workers in a local cloth mill, there was not a single case of cor pulmonale, although one would expect it in an industrial concern where dusty occupations were involved. By contrast, in a rural survey carried out in the village of Najafgarh, near Delhi, out of 729 cases examined there were 10 cases of cor pulmonale (1.3 per cent).

### *Etiologic Factors*

*Age.* The maximum incidence of the disease was between 30 and 59 years (table 3), the highest incidence being in the fifth decade. The youngest patient was 6 years old, a case of primary pulmonary hypertension and the second youngest one of pectus excavatum.

*Pulmonary Conditions.* Chronic bronchitis was the underlying cause in the largest number of patients. Pulmonary tuberculosis formed a low figure despite its high incidence in Delhi (table 4).

*Residence.* Of 119 patients whose addresses and permanent place of residence could be definitely verified, 68 belonged to rural and semirural areas, and 51 to the city of Delhi. By semirural areas are meant workmen's colonies and huts situated on the outskirts of Delhi city, which might be considered slums. Rural and semirural cases therefore accounted for 57 and urban for 43 per cent of cases. In the rural and semirural areas, the houses were mostly 1- or 2-roomed mud huts in which several members of the family lived together. There was no outlet for smoke with the result that the house was filled with smoke when the family meal was cooked. The city dwellers lived in small 1- or 2-roomed tenements, ill ventilated and overcrowded.

The fuel used almost universally is cow dung which is dried into flat cakes for this purpose. Probably from inadequate combus-

tion, it emits a lot of smoke. A recent survey estimated that cow dung provides as much as 90 per cent of power in India.

*Economic Status.* The 127 cases studied were distributed as follows: Low-socioeconomic class, income below 50 rupees per month, 100 cases—79 per cent. Middle class, income between 50 rupees and 250 rupees per month, 20 cases—16 per cent. High socioeconomic class, income 250 rupees and over per month, 7 cases—6 per cent.

*Occupation.* Of the adults, there were only 4 office workers. The female patients were all housewives. Those coming from the rural areas were part-time farm workers. One of the urban group worked in a canning factory. All the patients from the villages and some from the city gave a history of having spun cotton in their homes for varying periods. It was part of their daily life. Many of them had given it up only on becoming ill. A few of the semirural group had also done part-time stone breaking and grinding, but this work did not appear to be long enough to be a significant etiologic factor.

*Climate.* All the patients in this group were from Delhi and the neighboring districts. Delhi has a dry climate except for about 2 months in the monsoon season (rainfall 20 to 25 inches). In summer the temperature rises to 110 F. and in winter falls as low as 40 F. Dust storms are a daily feature for about 4 months of the year.

## Clinical Features

*Duration of Underlying Respiratory Disease.* Before the onset of failure, patients gave a history of symptoms referable to the underlying lung condition for a variable period of time (table 5). The total duration of symptoms was below 10 years in 68 per cent of cases. The shortest in this series was 8 months and the longest, 40 to 45 years (since childhood). The fact that a fairly large number (14 per cent) of patients gave a short history of less than 1 year might be partly attributed to their not paying much attention to minor respiratory complaints and not seeking medical aid. All these patients showed signs of marked pulmonary emphysema. In contrast, in the small number of patients from the higher socioeconomic group, symptoms dated back to childhood or usually at least 20 to 25 years.

Table 5.—*Duration of Pulmonary Symptoms*

| Duration | 1 yr. or less | 2—5 yrs. | 6—10 yrs. | 11—20 yrs. | More than 20 yrs. | Not definite |
|---|---|---|---|---|---|---|
| No. of patients | 18 | 33 | 35 | 18 | 16 | 7 |
| Percentage | 14.2 | 26.0 | 27.6 | 14.2 | 12.5 | 5.5 |

Table 6.—*Signs and Symptoms in 125 Patients in Congestive Heart Failure*

| Symptoms and signs | No. of patients | Percentage |
|---|---|---|
| Dyspnea | 125 | 100 |
| Orthopnea | 81 | 64.8 |
| Raised venous pressure | 110 | 88 |
| Edema | 113 | 90.4 |
| Enlarged liver | 125 | 100 |
| Ascites | 69 | 55.2 |
| Cyanosis | 104 | 83.2 |
| Mental confusion | 8 | 6.4 |

*Physical Findings (table 6).* All the cases presented primarily as gross congestive cardiac failure, with edema, hepatic enlargement, raised venous pressure, and ascites, but no special cardiac signs. It was really by the absence of signs of other heart disease and findings of gross pulmonary disease (emphysema, chronic bronchitis, and bronchiectasis) that the diagnosis was made. In Western countries, one is used to finding patients with a long history of emphysema from various causes developing slight ankle edema as the first manifestation of cardiac involvement, rather than this picture of severe acute congestive failure, which dominates all other symptoms.

Of the 127 cases in the present study, all but 2 were in frank congestive failure when first seen. One was a case of primary pulmonary hypertension, the other was admitted with chronic bronchitis, and right ventricular hypertension was diagnosed only on cardiac catheterization. Signs of congestive heart failure, especially right-sided, were very pronounced in all the cases.

*Signs of Pulmonary Disease.* There was evidence of gross pulmonary disease in all but 2 patients (cases of primary pulmonary hypertension) (table 4). Emphysema and coarse bubbling rales were present on admission in all these cases in

TABLE 7.—*Number of Attacks of Cardiac Failure before Death in Twenty-eight Patients*

| No. of attacks | 1 | 2 | 3 | More than 3 |
|---|---|---|---|---|
| No. of patients | 14 | 5 | 4 | 5 |
| Percentage | 50 | 17.85 | 14.3 | 17.85 |

TABLE 8.—*Heart Size (Cardiothoracic Ratio) in 119 Cases*

| C/T ratio in per cent | 50 | 55 | 60 | 65 | 70 and above |
|---|---|---|---|---|---|
| No. of patients | 12 | 36 | 39 | 23 | 9 |
| Percentage | 10.1 | 30.3 | 32.7 | 19.3 | 7.6 |

failure, indicating that pulmonary edema was a prominent feature of the heart failure. Bronchospasm was present, persistently in some cases and intermittently in others.

*Cardiac Findings.* There were no special cardiac signs. In fact the absence of signs of heart disease to account for the congestive heart failure associated with findings of gross pulmonary disease indicated the diagnosis of cor pulmonale. The heart size was enlarged in 90 per cent of cases but this enlargement could not be clinically ascertained in the majority, owing to emphysema. Correct assessment was made on fluoroscopy in 118 cases. The only notable findings pertaining to the heart were a loud pulmonic second sound in 65 per cent of cases and systolic murmur of grade I and II in 20 per cent and grade III in 4 per cent of cases.

*Associated Heart Disease of Other Types.* Benign hypertension was present in 5 cases. Left bundle-branch block was present in 2 cases, perhaps indicative of atherosclerotic heart disease. The physical signs and symptoms of these cases were those of cor pulmonale and not those of degenerative heart disease. These might have acted as contributory causes, however.

*Superadded Acute Respiratory Infection.* Fever was present on admission together with congestive heart failure in 33 per cent of the patients. It was not possible, except for fever, to make a definite diagnosis of superadded respiratory infection, which might have precipitated the congestive failure. Polymorphonuclear leukocytosis was present in 14 per cent of cases on admission, which might have been due to superadded respiratory infection.

*Mortality.* Twenty-eight patients (22 per cent) of this series died, 50 per cent of them during the first attack of failure. The rest lived for periods ranging from 6 months to 3 years after the first attack. The average duration of life after the first attack was 1 year and 7 months. The number of attacks of cardiac failure before death occurred is shown in table 7.

*Follow-up.* It was possible to follow up only 52 cases (41 per cent) out of this group of 127. The rest failed to report to the cardiac clinic after their discharge from hospital. Of these 28 died. Of the remaining 24, 6 cases (25 per cent) were alive at the end of 2 years and 3 cases (12.5 per cent) at the end of 3 years.

## LABORATORY FINDINGS

*Radiologic Features.* There were characteristic findings of emphysema in all cases, such as wide intercostal spaces, poor chest movements, depressed and flat diaphragms, increased bronchovascular markings, and evidence of the underlying lung disease.

The heart was enlarged in 90 per cent of cases in which x-rays and fluoroscopy were done. Table 8 gives the cardiothoracic ratios in this series. In many cases the enlarged heart shadow diminished as the heart failure resolved. The pulmonary conus was full in the posteroanterior view in 75 per cent of cases and in another 4 per cent it was prominent only in the right anterior oblique view. Right ventricular enlargement as judged by the oblique views was noted in 67 per cent and left ventricular enlargement in the left anterior oblique view was present in 22 per cent. The position of the heart was usually vertical. The markings of the pulmonary arteries at both hila were pronounced in all the cases.

*Electrocardiographic Findings.* The electrocardiograms of 101 patients were available for study. The conventional 12 leads were taken in all, $V_{3R}$ and $V_{5R}$ in 46 and $V_{3R}$ in 7 cases. The major abnormalities consisted of right deviation of the electric axis in 74 per cent, right ventricular hypertrophy[19-21] in 73 per cent, and T-wave changes in 27 per cent.

*Cardiac Catheterization Data.* Fifteen patients were submitted to right heart catheterization. All of them had recovered from congestive failure at the time of the procedure. Right ventricular and pulmonary artery resting pressures were considerably elevated in 11 patients (over 60 mm. Hg) and moderately in 4 (30-60 mm.).

Definite peripheral arterial unsaturation was present in 4 cases out of 6 in which arterial oxygen saturations were done. The cardiac output could not be accurately determined in these cases owing to inadequate facilities.

Although pulmonary artery pressures were elevated in all the cases, the electrocardiogram was normal in 5 and showed a pattern of left bundle-

branch block in 1. In 2 cases the pattern of the electrocardiogram changed from normal to pattern III later in the course of the disease.

*Hematologic Findings.* Twenty-five per cent of patients were anemic. As the majority of patients were from a low-socioeconomic group, poor diet could have been a contributory cause of anemia (table 9).

*Venous Pressure.* The jugular venous pressure was estimated in 92 cases (table 10). In 83 per cent of cases venous pressures above the normal values were recorded. Of the 16 patients with normal values 1 had never been in failure, 10 were in mild congestive failure and the other 6 in gross congestive failure.

*Autopsy Findings.* Permission for autopsy could be obtained in only 4 cases owing to the religious prejudice against autopsy (table 11). Representative pathologic changes are shown in figures 1 to 10.

TABLE 9.—*Hematocrit Values in 120 Cases*

| Hematocrit in cm. per cent | Below 42 | 42-45 | 46-50 | 51-60 | Above 60 |
|---|---|---|---|---|---|
| No. of patients | 31 | 34 | 29 | 18 | 8 |
| Percentage | 25.8 | 28.4 | 24.2 | 15.0 | 6.6 |

TABLE 10.—*Venous Pressure Readings in 92 Cases*

| Jugular venous pressure in cm. of water | 4-10 | 11-20 | 21-30 | 31-40 | Above 40 |
|---|---|---|---|---|---|
| No. of patients | 16 | 36 | 35 | 2 | 3 |
| Percentage | 17.6 | 39.6 | 38 | 2.1 | 3.2 |

## DISCUSSION

The outstanding feature of this series was the high incidence of cor pulmonale in an entirely nonindustrial population. Previous studies except from some parts of India[5] and from predominantly industrial populations[8] had shown a low incidence of this condition. Pneumoconiosis has been repeatedly stressed as the most important predisposing cause of all.[22]

Men and women were almost equally affected in the present study (1.2:1.0) unlike previous ones which recorded a high preponderance of males over females.[5, 6, 8, 22] The comparatively young age of these patients was another important feature. Fifty-six per cent of the patients were between the ages of 30 and 50 years and nearly a third (32 per cent) below 40 years. In White and Jones'[23] series all but 4 were more than 50 years old, and 13 were over 60. In Scott and Garvin's[14] series of 50 autopsy cases, 35 were over 50 years and 16 over 60.

The short duration of pulmonary symptoms was another striking feature. The majority of patients in this series had a history of pulmonary disease of less than 10 years. As many as 15 per cent had a history of less than 1 year's illness. In many cases a history of cough was elicited with difficulty on direct questioning. It is very probable that minor respiratory infections went unnoticed, owing to the general apathy of the patients who were extremely poor and in no position to pay attention to anything except a severe illness. This indifference has been noticed with regard to most ailments by those of us who have worked in the health center at Najafgarh, outside Delhi.

The very squalid living conditions and the smoke-filled atmosphere in which these patients lived were undoubtedly contributory factors to the rapid progress of the disease.

Rural patients predominated over urban in the ratio of 1.33:1.0. Although both groups came from extremely poor classes, this slight predominance is probably explained by the existence of even fewer medical facilities in the villages as compared to the city. In the rural and industrial surveys mentioned earlier cor pulmonale was also more prevalent in the former group. In the 1951 census it was estimated that in 72 villages around Delhi there was 1 doctor per 31,000 of population. In Delhi city on the other hand there is 1 doctor per 1,400 people. During history taking it was noticed that most of the rural patients admitted to having consulted a doctor for the first time while seeking admission to hospital for congestive heart failure. In the case of the

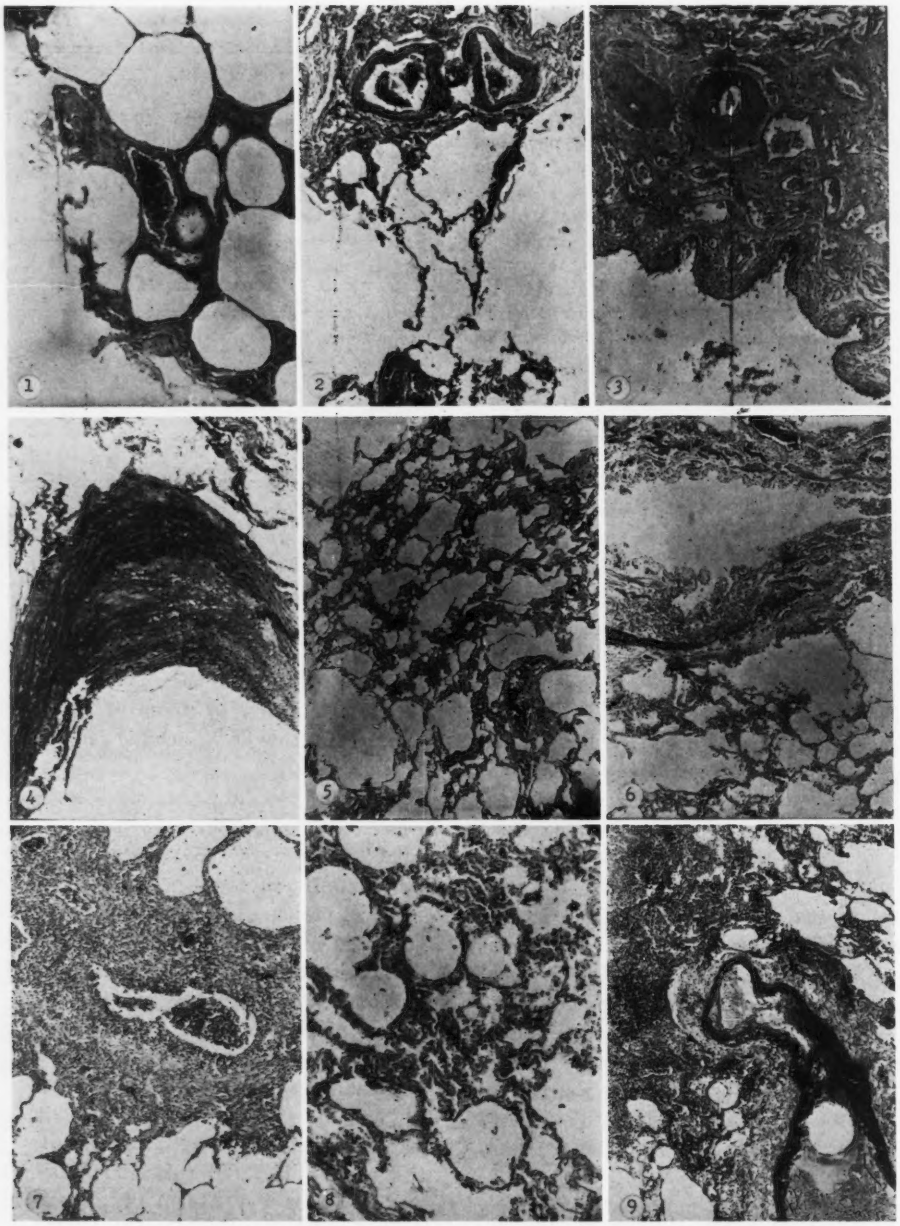

FIG. 1-9. *1.* CASE 2. Photomicrograph of lung showing thickening of alveolar walls. × 10. *2.* Case 1. Photomicrograph showing marked emphysema, thinning and avascularity of alveolar walls, and thick-walled medium-sized blood vessels. × 43. *3.* Case 1. Photomicrograph showing bronchiectasis and markedly thickened blood vessels with endarteritis and narrowing of lumina. × 48. *4.* Case 2. Photomicrograph showing atherosclerosis of pulmonary artery. × 10. *5.* Case 3. Photomicrograph showing marked emphysema with thickening of alveolar

*(Continued on bottom of next page)*

FIG. 10. Photograph of right and left ventricle. Right ventricular wall is thicker than the left.

city dwellers, many more had been to a doctor for treatment of respiratory infection at some time of their lives prior to the onset of congestive heart failure. It must however be admitted that even city dwellers had been seen by a physician on not more than a few occasions prior to the onset of congestive heart failure. The term "doctor" was confusing to these patients as there are 100 hakims and vaids (physicians practicing ancient Indian systems of medicine) and 65 homeopaths registered in Delhi (as against 900 doctors qualified in modern medicine).

In this series all the patients were in an advanced stage of cardiac involvement on their admission to hospital. As many as 125 out of 127 patients were admitted with gross signs of congestive heart failure. Cardiac enlargement was present in 90 per cent of cases. Electrocardiographic evidence of right ventricular hypertrophy was present in 75 per cent of cases, pointing to advanced disease. It is well known that the pattern of right ventricular hypertrophy is late in appearance in cases of cor pulmonale.[24] The high pressures in the right ventricle and pulmonary artery on catheterization in all the cases were also indicative of advanced disease.

The mortality figures in this study were probably low, as those patients who never came back for follow-up (59 per cent), probably died at home. This is surmised from the fact that in those who were followed up (41 per cent), frequent relapses of congestive heart failure were the rule. The average duration of life, after onset of congestive failure in this series was 1 year and 7 months, which resembles the figures given by Fulton.[25] The slightest change from strict bed rest or a minor respiratory infection precipitated another bout of failure.

Necropsy findings pointed to considerable pulmonary insufficiency due to severe emphysema, bronchitis, bronchiolitis, and bronchiectasis. The pulmonary findings in fact dominated the picture. There was involvement of the smaller blood vessels (atheroma) in 2 cases. Atheroma of the pulmonary artery was present in 3 cases out of 4 suggesting high pressure in the pulmonary circulation. It is all the more remarkable, for atheroma of the aorta was not present in these patients except minimal lesions in 1 (no. 4). The heart was enlarged in all, the lowest heart weight being 300 Gm. Although the thickness and weight of each ventricle separately was determined in

walls. × 55. *6.* Case 3. Photomicrograph showing bronchiectasis, anthracosis, and emphysema. × 57. *7.* Case 3 Photomicrograph of small area of lung parenchyma showing diffuse infiltration with chronic inflammatory cells and adenosis. × 57. *8.* Case 1. Photomicrograph showing marked emphysema with interstitial pneumonitis. × 90. *9.* Case 4. Photomicrograph of a normal medium-sized blood vessel and inflammatory changes in surrounding lung parenchyma. × 39.

TABLE 11.—*Summary of Autopsy Findings and Electrocardiographic Data in Four Cases*

| Lungs | CASE 1 | CASE 2 | CASE 3 | CASE 4 |
|---|---|---|---|---|
| Weight | Right—635 Gm.<br>Left—535 Gm. | Right—550 Gm.<br>Left—337 Gm. | Right—682 Gm.<br>Left—340 Gm. | Right—495 Gm.<br>Left—405 Gm. |
| Macroscopic appearances | Voluminous. Emphysematous. Right lung fibrosis marked | Voluminous due to emphysema. Firm pleural adhesions both lungs. Ruptured bulla right lung at apex. Consolidation right apex | Voluminous due to emphysema. Pleural adhesions both lungs | Emphysematous. Marked bilateral basal bronchiectasis. Pleural adhesions both sides |
| Microscopic appearances | *Alveoli*—Marked emphysema. Alveolar walls thickened. Some bronchopneumonia | *Alveoli*—Marked emphysematous change. Interstitial fibrosis and replacement fibrosis | *Alveoli*—Marked emphysematous change. Bronchopneumonia. Adenosis at places. Fairly marked fibrosis | *Alveoli*—Marked emphysematous change. Multiple small abscesses. Fibrosis |
| | *Bronchi*—Chronic purulent bronchitis and bronchiolitis. Mucosa atrophied | *Bronchi*—Chronic bronchitis and bronchiolitis. Mucosa denuded and muscle coat destroyed, at places | *Bronchi*—Bronchiectasis. Chronic purulent bronchitis and bronchiolitis | *Bronchi*—Dilated wall markedly thinned. Purulent bronchitis |
| | *Blood vessels*—Atherosclerosis of large and medium-sized vessels. Patchy raising of intima with thickened subintimal tissue. Small blood vessels show uniform intimal thickening. Lumina narrowed. Media normal | *Blood vessels*—Smaller vessels normal. Bigger vessels show atherosclerosis | *Blood vessels*—Essentially normal | *Blood vessels*—Smaller vessels show subintimal thickening |
| Heart weight | 389 Gm. | 372 Gm. | 300 Gm. | 335 Gm. |
| Ventricles | RV hypertrophied compared to LV. Cavity dilated. Tricuspid orifice 13.7 Gm. | RV hypertrophied. Cavity dilated | Right ventricle thin walled and cavity dilated | RV—110 Gm.<br>Wall 1.3 cm. thick.<br>Cavity dilated |
| | LV normal in thickness | Left ventricular cavity dilated. Thickness normal | Left ventricular cavity dilated | LV—95 Gm.<br>Wall 1 cm. thick |
| Coronary arteries and aorta | Normal | Normal | Normal | Few atheromatous plaques in aorta |
| Pulmonary arteries | Atheromatous lesions | Atheromatous lesions | ——— | Atheromatous patches |
| Electrocardiographic data | RVH. Diffuse T-wave changes in precordial leads | RVH. Diffuse T-wave changes in precordial leads | Not done | RVH. Diffuse T-wave changes |

only 1 case, the heart weight was increased in all cases, and the right ventricular wall thickened and the cavity dilated in all the cases. Right ventricular hypertrophy resulted, presumably, from the greatly diminished vascular bed secondary to the emphysema, which was a striking feature in all the cases. Pulmonary fibrosis was not a prominent feature.

It seems reasonable to conclude that the high incidence of cor pulmonale in Delhi is the result of emphysema secondary to widespread chronic respiratory infections that go untreated owing to lack of medical facilities and to the poverty of the people.

No other factors could be held responsible in this study. Whether the high incidence as reported from other parts of India is due to the same cause, it is not possible to say.

## Summary

A high incidence of cor pulmonale was noted in Delhi in an entirely nonindustrial population. Men were only slightly more affected than women and there was a preponderance of rural over urban cases.

The patients were comparatively young, gave a short history of the underlying pulmonary disease, and presented with very florid signs of congestive heart failure on their first visit to hospital.

The cardiac involvement was considerably advanced in all cases as judged by electrocardiographic and cardiac catheterization data.

Four cases came to autopsy and the findings showed advanced pulmonary disease with right ventricular hypertrophy.

It is postulated that this high incidence of cor pulmonale was the result purely of chronic respiratory infections that had remained untreated owing to lack of medical facilities and the extreme poverty of the people.



## Acknowledgment

We gratefully acknowledge the assistance of the Pathology Department of Lady Hardinge Hospital.



## Summario in Interlingua

Un alte incidentia de corde pulmonal esseva notate in Delhi in un population completemente non-industrial. Le masculos esseva afficite a grados solmente pauco plus alte que le famininas, e le casos ab areas rural proponderava in comparation con illos ab areas urban.

Le patientes esseva comparativemente juvene. Le historia del subjacente morbo pulmonar non esseva prolongate. Le patientes se presentava con floridissime signos de congestive disfallimento cardiac al tempore de lor prime vista al hospital.

Le affection cardiac esseva multo avantiate in omne le casos, a judicar per datos electrocardiographic e catheterisatori.

Quatro casos esseva studiate necropticamente. Illos exhibiva signos de avantiate morbo pulmonar con hypertrophia dextero-ventricular.

Es postulate que iste alte incidentia de corde pulmonal esseva le resultato exclusive de chronic infectiones respiratori que habeva remanite sin tractamento a causa del absentia de facilitates medical e a causa del extreme pauperitate del gente.


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From which observations with good reason we may gather that the heart at that time whilst it is in motion, suffers constriction, and is thickned in its outside, and so streightned in its ventricles, thrusting forth the blood contained within it: which from the fourth observation is evident, because that in the tention it becomes white, having thrust out the blood contained within it, and presently after in its relaxation and rest a purple and crimson colour returns to the heart. But of this no man needs to make any further scruple, since upon the inflicting of a wound into the cavity of the ventricle, upon every motion and pulsation of the heart, in the very tention, you shall see the blood within contained to leap out.—William Harvey. *De Motu Cordis*, 1628.

# Cardiovascular Responses in Experimentally Induced Alterations of Affect

*By* MORTON D. BOGDONOFF, M.D., JOSEPH J. COMBS, JR., M.D., GERALD D. N. BRYANT, M.D., AND JAMES V. WARREN, M.D.

Although alterations in emotional arousal have long been associated with changes in cardiovascular dynamics, the precise quantitative relationship has not been fully detailed. Independent assessment of the emotional change was felt to be a necessary component of a quantitatively oriented study. The variously described responses for "anxiety" and "anger" might better be re-explored in such a manner. The emotional arousal was experimentally produced in the laboratory. Measures of pulse, arterial blood pressure, and cardiac output were conducted both before and during the change in affect evoked by the laboratory stimulus.

SINCE the early studies of Cannon,[1] psychological activity has been considered an important determinant of the level of cardiovascular function. In ensuing years, much research has been conducted in psychological and physiologic laboratories amplifying Cannon's observations. Relatively few studies, however, have been carried out in which such relationships have been systematically assayed employing experimentally induced alterations of affect and more recently available hemodynamic technics. We have, therefore, carried out such a study on a group of normal human subjects.

## METHODS AND SUBJECTS

Young male volunteer university students were studied. They were solicited by the laboratory as subjects for experiments involving psychological factors and paid a fee for the study. Measurement of cardiac output was determined by the multiple sample dye technic of Hamilton et al.[2] as modified by Doyle et al.,[3] but with superior vena caval injection of dye. Arterial pressure was recorded via a needle inserted in the brachial artery and by means of a strain-gage transducer and multiple-channel photographic system. Mean pressure levels were determined by electronic integration. Respiratory excursions were recorded by a pneumotachograph. Electrocardiogram was recorded as a standard lead II. All studies were carried out with the subject in the supine position.

The technics used in the study of affect involved 2 phases: the production of affect alteration, and the assay of the actual nature of the affect alteration that was produced. The sequence of events incorporated in an experimental run is given and indicates the time relationships of the various phases of the study: 1. Arrival of subject in laboratory; preparation of subject by nurse; subject lies quietly in supine position for 15 to 30 minutes before experimenters arrive. 2. Insertion of needles into artery and vein; adjustment of recording equipment; elapsed time 30 to 45 minutes. 3. Following 10 minutes of quiet, initial cardiac output measured (output #1). 4. Following another 10-minute period of rest and quiet, second cardiac output measured (output #2). 5. Period of affect production conducted, lasting 5 to 10 minutes. At the very end of this period, "stimulatory" cardiac output measured (output #3). 6. Experimental personnel leave laboratory; interviewer enters and conducts interview focusing on subject's affect during stimulus period.

### *Affect Production*

Two types of stimuli were used: role enactment and electric shock. The role enactment procedures consisted of the experimenters either creating an atmosphere of concern about the subject's welfare or accusing the subject of failing to cooperate properly. Concern about the subject's welfare focused on alterations in the subject's heart. A representative exchange was as follows: Experimenter no. 1: "The heart tracing looks off." Experimenter no. 2: "Yes, something definitely

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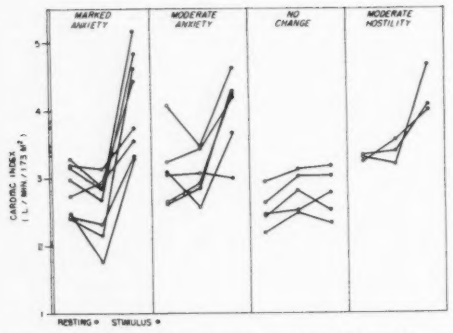


FIG. 1. Resting and stimulus cardiac indices in normal male subjects, grouped according to the evaluation of affect change associated with the stimulus response.

must be wrong. How do you feel? Better check him again or call the chief. It may be necessary to have him on hand." The experimenter would then check all equipment, auscultate the heart, and make several references to "something just isn't quite right . . . . we may need help . . . " The nurse was asked to check certain observations. Factors and references were made about the subject's appearance, pulse, and blood pressure, all indicating concern of the experimenters. After 5 to 10 minutes of this role enactment, the cardiac output was determined. Following this stimulus, the subject was reassured.

The role enactments focusing on the subject's failure to cooperate properly consisted of the experimenters repeatedly asking the subject to hold perfectly quiet. When some bodily motion occurred, the experimenters expressed disapproval and annoyance. When no bodily motion occurred, the subject was told that he was not properly relaxing and that his muscles were too tense. The subject was again accused of failure to do what he was asked. The stimulus cardiac output determination was made after 5 to 10 minutes of such exchange.

Electric shock stimulus consisted of the application of an electrocardiographic lead plate to the lower extremity with the connection made to a small rheostat signaling a 5-volt, 5-ampere stimulus. The electric shock was intermittently and unpredictably administered and impulses lasted from 1 to 2 seconds, occurring every 3 to 10 seconds for a 1- to 3-minute period. During the electric stimulus application, the patient was told the whole purpose of the experiment failed if the shocked extremity moved. The experimenter expressed annoyance when this occurred, and the subject was told he was not fully cooperating. Following the last electric shock, a stimulus output determination was made.

*Affect Measurement*

Immediately following the stimulus cardiac output determination (output #3), a focused interview was conducted. This was the major technique employed in judging the quality of affect that attended the stimulus.

The interview was conducted by one of us in a directive manner. The opening phrases indicated the purpose of the interview. The questions were then directed to having the subject relate his feeling state during the stimulus as well as during the prestimulus periods. The opening questions were: "Could you tell us how you felt during the procedure" and "would you focus on your feeling state when you came to the laboratory and as the experiment went along?" The interviewer attempted to have the subject comment on the entire experiment including the rest periods and any and all procedures that occurred. The interview was recorded on a wire recorder and later reviewed for content.

The specific affect occurring during the stimulus period was judged in comparison with the control periods and with the inherent quality of the stimulus affect itself. Two major kinds of affect qualities were rated: anxiety and hostility. Intensity of the feeling state was judged by the interviewer from the verbal statements and by the subject's nonverbal expressions observed during the interview. A range scale of 1 to 4 plus was used. A stimulus affect rating of "no change" was also considered, and this rating was given to an evaluation in which no clear-cut expression of affect alterations could be detected. Results of the output studies were not known to the experimenter conducting the focused interview.

## RESULTS

*Psychological*

Twenty-two studies were carried out on 20 subjects. Seventeen stimulus periods consisted of verbal content and 5 of electric shock in addition to verbal content. Table 1 lists the results of all studies, grouped according to the quality and quantity of affect change noted. Eight experimental runs were rated as being attended by marked anxiety (group I), 6 runs by moderate anxiety (group II), 5 runs by no change (group III), and 3 runs by hostility of moderate degree (group IV). Responses to verbal and electric shock stimuli are represented in all groups except group III, which included only experimental runs in which verbal stimuli occurred.

TABLE 1.—*Cardiac Index, Heart Rate, Stroke Volume, Central Blood Volume, and Blood Pressure Observations*

| Subject stimulus* | Period | Cardiac index (L./min./1.73 M.²) | Cardiac index (r2—s) change (%) | Heart rate (beats/min.) | Stroke volume (ml./beat) | Central blood volume (L.) | Blood pressure (mm. Hg.) | Mean arterial B.P. (mm. Hg.) |
|---|---|---|---|---|---|---|---|---|
| Group I | | | | | | | | |
| 1 R. E. | r 1 | 3.27 | | 65 | 93 | 2.34 | 128/70 | 90 |
| | r 2 | 2.89 | | 67 | 79 | 2.13 | 130/70 | 90 |
| | s | 4.46 | +54 | 92 | 75 | 2.04 | 156/74 | 106 |
| 2 R. E. | r 1 | 2.46 | | 61 | 86 | 1.57 | 125/65 | 85 |
| | r 2 | 2.31 | | 60 | 82 | 1.58 | 129/67 | 87 |
| | s | 3.32 | +44 | 73 | 97 | 1.67 | 154/69 | 98 |
| 3 R. E. | r 1 | 2.44 | | 68 | 71 | 1.88 | 128/72 | 90 |
| | r 2 | 2.16 | | 68 | 65 | 1.66 | 128/70 | 90 |
| | s | 4.62 | +113 | 62 | 148 | 2.18 | 144/78 | 96 |
| 4 R. E. | r 1 | 2.97 | | 66 | 86 | 2.04 | 116/64 | 82 |
| | r 2 | 2.69 | | 70 | 74 | 1.60 | 116/64 | 82 |
| | s | 4.83 | +80 | 84 | 110 | 1.79 | 146/78 | 100 |
| 5 R. E. | r 1 | 2.74 | | 60 | 80 | 1.65 | 112/58 | 76 |
| | r 2 | 2.92 | | 52 | 99 | 1.84 | 114/60 | 78 |
| | s | 3.55 | +22 | 62 | 101 | 1.93 | 124/64 | 84 |
| 6 E. S. | r 1 | 2.47 | | 58 | 86 | 1.94 | 120/66 | 84 |
| | r 2 | 1.74 | | 62 | 57 | 1.83 | 114/62 | 80 |
| | s | 3.30 | +90 | 88 | 76 | 2.11 | 126/70 | 88 |
| 7 E. S. | r 1 | 3.18 | | 62 | 98 | 1.88 | 125/73 | 91 |
| | r 2 | 3.14 | | 56 | 107 | 1.86 | 131/77 | 94 |
| | s | 3.74 | +19 | 72 | 99 | 1.84 | 141/85 | 104 |
| 8 R. E. | r 1 | 3.17 | | 60 | 100 | 1.97 | 124/62 | 84 |
| | r 2 | 2.84 | | 58 | 93 | 1.78 | 126/70 | 91 |
| | s | 5.16 | +81 | 82 | 119 | 1.82 | 150/76 | 100 |
| Means | r 2 | 2.58 | | 60 | 70 | 1.78 | 123/68 | 87 |
| | s | 4.12 | +63 | 77 | 88 | 1.91 | 143/74 | 97 |
| Group II | | | | | | | | |
| 9 R. E. | r 1 | 2.65 | | 53 | 91 | 1.68 | 105/55 | 70 |
| | r 2 | 2.91 | | 51 | 103 | 1.68 | 103/55 | 67 |
| | s | 4.25 | +46 | 61 | 127 | 1.83 | 110/50 | 70 |
| 10 R. E. | r 1 | 3.05 | | 78 | 73 | 1.68 | 96/52 | 71 |
| | r 2 | 3.08 | | 72 | 80 | 1.66 | 100/54 | 71 |
| | s | 3.00 | —1 | 82 | 68 | 1.68 | 108/81 | 67 |
| 11 R. E. | r 1 | 3.24 | | 76 | 76 | 1.82 | 106/52 | 69 |
| | r 2 | 3.44 | | 68 | 90 | 1.68 | 104/48 | 66 |
| | s | 4.20 | +22 | 92 | 81 | 1.80 | 118/52 | 62 |
| 12 E. S. | r 1 | 2.64 | | 62 | 75 | 1.73 | 110/62 | 80 |
| | r 2 | 2.85 | | 62 | 81 | 1.60 | 106/60 | 76 |
| | s | 4.27 | +50 | 70 | 108 | 1.79 | 123/76 | 86 |
| 13 E. S. | r 1 | 3.05 | | 60 | 84 | 1.93 | 148/67 | 87 |
| | r 2 | 2.58 | | 68 | 63 | 1.57 | 130/76 | 93 |
| | s | 3.66 | +41 | 80 | 75 | 2.65 | 141/74 | 93 |
| 14 R. E. | r 1 | 4.09 | | 74 | 110 | 2.18 | 140/80 | 99 |
| | r 2 | 3.49 | | 72 | 97 | 2.01 | 134/74 | 94 |
| | s | 4.64 | +33 | 82 | 112 | 1.08 | 147/82 | 104 |
| Means | r 2 | 3.06 | | 66 | 86 | 1.70 | 113/61 | 78 |
| | s | 4.00 | +32 | 78 | 95 | 1.80 | 131/69 | 80 |

*(Continued on next page)*

TABLE 1.—Continued

| Subject stimulus* | Period | Cardiac index (L./min./1.73 M.²) | Cardiac index (r2—s) change (%) | Heart rate (beats/min.) | Stroke volume (ml./beat) | Central blood volume (L.) | Blood pressure (mm. Hg.) | Mean arterial B.P. (mm. Hg.) |
|---|---|---|---|---|---|---|---|---|
| Group III | | | | | | | | |
| 15 R. E. | r 1 | 2.63 | | 76 | 62 | 1.73 | 116/64 | 81 |
| | r 2 | 3.03 | | 70 | 78 | 1.67 | 120/66 | 84 |
| | s | 3.03 | 0 | 72 | 75 | 1.57 | 156/74 | 98 |
| 16 R. E. | r 1 | 2.20 | | 56 | 77 | 1.67 | 136/64 | 80 |
| | r 2 | 2.50 | | 56 | 88 | 1.78 | 136/70 | 82 |
| | s | 2.34 | —7 | 62 | 74 | 1.71 | 136/76 | 100 |
| 17 R. E. | r 1 | 2.95 | | 74 | 89 | 2.14 | 110/60 | 77 |
| | r 2 | 3.14 | | 78 | 90 | 2.09 | 112/64 | 80 |
| | s | 3.18 | 0 | 84 | 85 | 2.13 | 116/66 | 88 |
| 18 R. E. | r 1 | 2.48 | | 56 | 87 | 1.92 | 136/77 | 96 |
| | r 2 | 2.50 | | 52 | 94 | 1.72 | 144/82 | 102 |
| | s | 2.79 | +6 | 60 | 91 | 1.93 | 150/80 | 98 |
| 19 R. E. | r 1 | 2.48 | | 64 | 90 | 1.99 | 120/68 | 85 |
| | r 2 | 2.81 | | 58 | 97 | 1.82 | 116/66 | 84 |
| | s | 2.53 | —8 | 64 | 79 | 1.86 | 136/80 | 98 |
| Means | r 2 | 2.80 | | 63 | 89 | 1.82 | 126/69 | 86 |
| | s | 2.77 | —2 | 68 | 81 | 1.84 | 140/75 | 96 |
| Group IV | | | | | | | | |
| 20 R. E. | r 1 | 3.26 | | 87 | 66 | 1.34 | 121/67 | 83 |
| | r 2 | 3.59 | | 90 | 70 | 1.53 | 125/65 | 83 |
| | s | 4.02 | +12 | 100 | 71 | 1.37 | 137/71 | 94 |
| 21 E. S. | r 1 | 3.32 | | 64 | 99 | 1.79 | 114/60 | 78 |
| | r 2 | 3.23 | | 60 | 102 | 1.85 | 110/60 | 77 |
| | s | 4.70 | +45 | 82 | 109 | 2.10 | 136/67 | 87 |
| 22 R. E. | r 1 | 3.31 | | 78 | 80 | 1.84 | 116/63 | 80 |
| | r 2 | 3.42 | | 62 | 104 | 1.92 | 109/61 | 78 |
| | s | 4.14 | +21 | 86 | 91 | 2.10 | 139/84 | 101 |
| Means | r 2 | 3.41 | | 70 | 92 | 1.77 | 115/62 | 79 |
| | s | 4.22 | +26 | 89 | 90 | 1.86 | 134/74 | 94 |

*Abbreviations: R. E., role enactment; E. S., electrical stimulus; r 1, resting period #1; r 2, resting period #2; s, stimulus period.

*Cardiovascular (fig. 1)*

*Group I.* Marked Anxiety: Cardiac index increased most markedly in this group (+63 per cent). An increase in both heart rate and stroke volume almost always contributed to this change in cardiac output. Two exceptions to this pattern were subject 1 who had a rise of 25 beats per minute in heart rate and a decrease of stroke volume of 4 ml. per minute, and subject 3 who had a decrease of 6 beats per minute in heart rate but an increase in stroke volume of 83 ml. per minute. No other specific characteristics of these individuals could be ascertained to explain the variation of these responses. There was a consistent increase in mean arterial blood pressure (+10 mm. Hg). There were no consistent changes in central blood volume.

*Group II.* Moderate Anxiety: Cardiac index increased less markedly in this group (+32 per cent) than in group I. Heart rate

increase always occurred. Stroke volume increases did not occur in 2 individuals (subjects 10 and 11), in one of whom (10) cardiac output did not increase. Mean arterial pressure did increase (+2 mm. Hg), although this change was not as consistent in this group. There was no change in central blood volume.

*Group III.* There was no significant change in cardiac index. There was consistent increase in mean arterial pressure (+10 mm. Hg). There was no change in central blood volume.

*Group IV.* There was an increase in cardiac index (+26 per cent) and an increase in mean arterial pressure (+15 mm. Hg), but no change in central blood volume.

## Discussion

A major problem in experiments of this type is the production and evaluation of the induced alteration of affect. The technics of role enactment and verbal stimuli depend upon interpersonal reactions and are difficult to make exactly the same for each experimental subject. Further, even if complete uniformity of stimuli were obtained, the individual's response would most likely vary, being dependent upon such factors as perception, association, and anticipation. It should be pointed out, therefore, that although every attempt was made to apply the same stimulus to the subjects in this study, it is to be expected that the disturbance of affect would vary from subject to subject. For this reason, it was important to attempt a quantitation of the affect change by independent technics.

Affect quality and intensity may be measured in a variety of ways. For the purposes of this study, the focused interview was chosen as most useful. By this means, the interviewer attempts to assay the type and intensity of affect response as recounted by the subject immediately following the experience. This technic depends upon the subject's ability to recall the experience, his ability to disclose his feelings, and the interpretation of the subject's statements by the interviewer. Although we were not able to control rigorously all these variables, the technic has proved useful in permitting us to quantitate affect measurement. It should be indicated that this interview is not intended to provide a profile of the personality type of the individual under observation but merely determines the affect state at the time of the experiment. The results of these interviews were matched against the hemodynamic observations.

The results reported here indicate that the intensity of affect may be directly correlated with the change in cardiac output and heart rate. Previous studies have indicated that anxiety, not purposefully induced, as evidenced by some subjects undergoing cardiac catheterization, was associated with marked cardiac output changes and increases in arterial pressure.[4] Our observations parallel these studies but have in addition afforded us the opportunity to isolate the experimentally induced affect change from a period of relative composure in the same experimental subject. More recently, additional direct Fick cardiac output measurements on anxious patients have been reported, but in only one was the cardiac output during anxiety compared to that of composure in an individual without cardiovascular disease.[5] The remainder of that report deals with the effect of induced anxiety on the ballistocardiographically determined cardiac outputs of normal human subjects. Our data, therefore, extend this information by more direct circulatory measurements and serve to verify the ballistocardiographic findings. In another report utilizing ballistocardiographic methods, the cardiac output response to exercise was found to be greater in anxious subjects than in relaxed ones.[6] Insofar as we are aware, no previous observers have attempted an independent measure of affect intensity and later a correlation with a direct measurement of cardiac output and other circulatory measurements.

It is important to note that the mean cardiac indices during stimulus of groups I,

II, and III are significantly different when analyzed statistically. Since the subjects were not chosen at random, and since the resting values were not similar in all subjects, the technic of analysis of covariance was employed.[7] The differences between the means were significant at the less than 1 per cent level. The means of the cardiac indices, adjusted for regression and resting differences, were group I, 4.27; group II, 3.78; group III, 2.76. This demonstration of significant difference between these groups would appear to contribute further confirmation of the correlation of affect intensity and magnitude of psychologic response.

These studies also indicate that the quality of affect, such as anxiety or hostility, may not be differentially related to the circulatory response. Previous observations on cuff-measured blood pressure responses and ballistocardiographic patterns in relation to alteration in affect states indicate some difference[8] in circulatory response, and in others, a similarity.[9] The results reported here indicate that under the conditions of our experimental situation, the pattern of cardiovascular response cannot be distinguished in the 2 affect states.

In those subjects displaying little or no evidence of direct alteration, the question arises as to whether the stimulus has been truly effective. It is interesting to note in this light that in the entire group of subjects under stimulation, there was a consistent although minimal rise in mean arterial pressure. This was independent of the quality or the quantity of the affect. The exact significance of this is not clear, but it would appear to indicate that the stimulus had at least some impact on circulatory regulation.

These observations raise the interesting question of whether the circulatory response is a secondary phenomenon, appearing as a result of the induced affect state, or whether it is an integral part of that state and, indeed, partly responsible for the subject's feeling of "anxiety." The observations reported here are consistent with either hypothesis.

It has long been thought that the autonomic nervous system and the adrenal glands play an important role in the body's response to anxiety and hostility. The observations reported here may be explained on this basis. The minimal pressor response that occurred in all experimental situations may be interpreted as evidence of a mild norepinephrine type of response. Superimposed upon this, in those subjects developing affect changes, are responses that may be interpreted as evidence of epinephrine-like activity: heart rate and stroke volume increases. It is hoped that in the future, additional studies of the type reported here can be carried out in association with chemical assays of these hormones in blood samples taken during the period of affect change.


## Summary

In a group of normal subjects, the intensity of affect change (anxiety or hostility) induced by experimental means correlates moderately well with the quantitative degree of change in cardiac output. The quality of affect does not appear to be related to the hemodynamic changes induced in these experiments. In all subjects exposed to psychologic stimulation, a minimal but definite increase in mean arterial pressure was noted.



## Acknowledgment

The authors are indebted to Dr. David M. Shaw for his invaluable assistance in preparing the statistical analysis of the data.



## Summario in Interlingua

In un gruppo de subjectos normal, le intensitate de alterationes del stato de affectivitate (anxietate o hostilitate), inducite per medios experimental, monstrava un correlation moderatemente bon con le grado quantitative de alteration in le rendimento cardiac. Le qualitate del stato affective non pare esser relationate con le alterationes hemodynamic indicite in iste experimentos. In omne le subjectos exponite a stimulos psychologic, un augmento minimal sed definite esseva notate in le valor medie del tension arterial.

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**John Wesley**

**Physician and Apothecary**

Wesley also had a considerable bone to pick with the apothecaries. About them he writes, "I am sensible, I may be esteemed wanting of sense if not of modesty, to contradict the skillful in their own art. Yet I cannot help it when either souls or lives of men are at stake." The medicines listed in "Primitive Physic," Wesley emphasized, were "pure, genuine, cheap, safe, easy to be applied and procured by the unlettered. Who can be sure of this when they are compounded in an apothecary? Perhaps he does not have the one ordered by the physician and puts in its place inferior ingredients. Or perhaps he has it, but it is stale and perished." He, therefore, urged the patient to procure his own medicine directly from the chemist. From his prescriptions, because of the danger, Wesley omitted the four Herculean medicines: (1) opium (2) Peruvian bark (cinchona) (3) steel and (4) preparations of quicksilver (mercury).

The specific remedies presented by Wesley have, of course, long been replaced by more effective ones. But many of his observations on food, water, manner of living, and attitudes toward life, the effect of prayer and emotions on the body and mind have truly stood the test of time.—Alfred A. Weinstein. *John Wesley Physician and Apothecary.* The Georgia Review **10**: 3, 1956.

# Effect of Mitral Valvulotomy on Tricuspid Insufficiency Associated with Mitral Stenosis

*By* Pier Federico Angelino, M.D., Beniamino Lo Bue, M.D., and Valeria Levi, M.D.

Twenty patients, affected by mitral disease associated with tricuspid insufficiency and selected for mitral commissurotomy on the basis of clinical evidence of advanced heart disease, have been studied before and after surgery. The further course of the disease could be related to various clinical and pathophysiologic conditions, the importance of which in the selection of patients is stressed.

TRICUSPID lesions are less common as isolated valvular diseases than in association with a more severe involvement of other valves.

The incidence of tricuspid involvement in rheumatic mitral disease has been reported to be frequent, but statistics are extremely variable on this point, due to the difficulty in having a diagnosis unequivocally confirmed,[1-11] at least as far as tricuspid lesions of lesser degree are concerned.

The possibility of surgical correction of the mitral valve increases the importance of recognizing the nature and type of combined valvular lesions. While no doubts exist as to some contraindications to mitral valvulotomy (severe mitral and aortic insufficiency, persistence of rheumatic activity, etc.), there are some other associated conditions the importance of which in the selection of patients is not well established. Among these are tricuspid lesions coexisting with pure mitral stenosis or with combined mitral stenosis and insufficiency. Pure tricuspid stenosis may be corrected surgically.[5, 9-11] As to tricuspid insufficiency, there are as yet no surgical technics for its direct treatment, and in many instances medical care is ineffective. Since tricuspid insufficiency can be reduced by hemodynamic improvement in pulmonary circulation, mitral valvulotomy should be considered as an indirect treatment.

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This report concerns the outcome after mitral commissurotomy in patients with associated tricuspid insufficiency. Particular attention is given to those hemodynamic factors that seem to have greater importance in the further course of the operated patients.

## Materials and Methods

During the 6-year period from 1951 to 1956, at the Heart Surgery Center in Turin, more than 2,000 patients affected by valvular disease, mostly mitral stenosis with or without insufficiency, were operated upon. This survey is restricted to the 20 patients who had tricuspid insufficiency in addition to mitral disease. The tricuspid damage was always severe, and quite often it was responsible for the majority of the symptoms. Eleven of the patients were females and 9 were males, and their ages varied between 21 and 45 years. All had advanced heart disease: 14 were in class IV, and 6 in class III, according to the criteria of the New York Heart Association. The subjects were divided in 2 groups: In group I were 13 patients with pure mitral stenosis (table 1); in group II were 7 with associated variable degrees of mitral insufficiency (table 2).

As to the tricuspid involvement, insufficiency was confirmed during operation in 18 patients, a systolic regurgitation being clearly perceived by the surgeon's finger inserted into the right atrium. In 2 additional cases tricuspid insufficiency was associated with tricuspid stenosis; the latter was corrected by tricuspid valvulotomy.

All patients exhibited symptoms of tricuspid insufficiency. The liver was enlarged in all instances, with definite systolic pulsations in 13 cases; cervical veins were engorged in all subjects, a systolic pulsation being visible in 13; ascites had been previously noted in 5 cases and in 2 it was present during hospitalization.

Auscultatory findings were those of mitral disease; moreover, tricuspid involvement produced

TABLE 1.—*Clinical Findings in Thirteen Patients with Pure Mitral Stenosis and Tricuspid Insufficiency, Group I*

| Age | Sex | Rheumatic fever | Dyspnea | Pulmonary edema | Hemophthisis | Ascites | Heart failure | Liver enlargement | Peripheral edema |
|---|---|---|---|---|---|---|---|---|---|
| 31 | M | yes | ++++ | + | +++ | — | ++ | +++ | + |
| 28 | F | yes | ++ | — | + | — | + | ++ | + |
| 28 | M | no | +++ | — | ++ | — | ++ | +++ | + |
| 24 | F | yes | +++ | + | — | — | +++ | ++ | + |
| 21 | F | yes | + | — | — | — | — | + | — |
| 45 | M | yes | ++++ | — | — | — | +++ | ++++ | ++ |
| 45 | F | yes | ++++ | — | + | +++ | +++ | ++++ | ++ |
| 29 | F | yes | ++ | — | + | ++ | +++ | +++ | ++ |
| 36 | M | yes | ++ | + | — | — | + | ++ | + |
| 37 | M | yes | +++ | ++ | ++ | + | ++++ | ++++ | +++ |
| 40 | F | yes | ++++ | + | + | + | ++++ | +++ | ++ |
| 42 | M | yes | +++ | + | ++ | — | ++ | ++ | + |
| 43 | M | yes | +++ | — | ++ | — | +++ | +++ | ++ |

TABLE 2.—*Clinical Findings in Seven Patients with Mitral Regurgitation and Tricuspid Insufficiency, Group II*

| Age | Sex | Rheumatic fever | Dyspnea | Pulmonary edema | Hemophthisis | Ascites | Heart failure | Liver enlargement | Peripheral edema |
|---|---|---|---|---|---|---|---|---|---|
| 31 | M | yes | ++++ | — | — | — | ++ | ++ | + |
| 28 | F | yes | ++ | — | — | ++++ | + | +++ | ++ |
| 40 | F | yes | ++ | — | — | + | ++ | ++ | + |
| 37 | M | yes | +++ | — | + | — | + | ++ | — |
| 21 | F | yes | ++ | ++ | — | — | ++ | +++ | ++ |
| 36 | F | yes | ++ | ++ | — | — | ++ | +++ | + |
| 38 | F | yes | ++ | + | — | +++ | ++++ | +++ | ++ |

a systolic murmur over the lower end of the sternum: its increase in intensity after a deep inspiration could not be observed in all patients.[12] Roentgen examination and angiocardiograms[13] revealed enlargement of right atrium and ventricle in both groups (fig. 1); moreover, additional enlargement of left cavities was revealed in group II. Sixteen patients had atrial fibrillation. Electrocardiographic evidence of combined ventricular hypertrophy was present in 6 patients of group I, while all other patients showed only right ventricular hypertrophy.

At operation in all subjects of group I, a severe degree of mitral stenosis was found (0.4-0.8 cm.$^2$); the area of the valve orifice after commissurotomy was about 3 to 3.5 cm.$^2$

Patients of group II, in whom a preoperative diagnosis of associated mitral insufficiency was made, were operated upon: in 2 of them a plastic repair of the mitral insufficiency was also attempted.

Clinical, radiologic, and electrocardiographic examinations were systematically made within 6 months and up to 2 years after operation, in order to evaluate further modifications of cardiocirculatory function.

## RESULTS

### *Postoperative Course*

In the first postoperative week, clinical conditions did not differ significantly in the 2 groups. Fifteen patients had a certain improvement of dyspnea, but hepatic enlargement and jugular venous engorgement were practically unchanged, except in 3, who

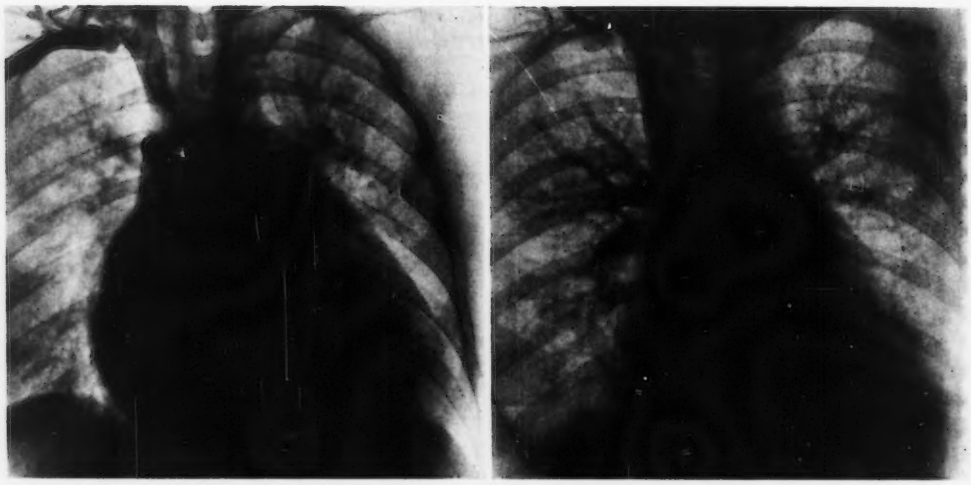

FIG. 1 *Left.* Dextrocardiogram made at 5 seconds in a patient with mitral stenosis and severe tricuspid insufficiency, showing marked enlargement of the right atrium and moderate opacification of the right ventricle. Compare this picture with the dextrocardiogram of a patient with pure mitral stenosis (*Right*), revealing a smaller right atrium and a uniform opacification of right atrium and ventricle.

showed only for a few days a less engorged liver. Five patients, including 1 with mitral insufficiency, had a normal postoperative course, as is usually observed in patients with pure mitral stenosis.

*Late Results*

The late results have been quite different in the 2 groups (table 3).

*Group I.* Also among the patients of this group, the results have been quite variable. Three of them had considerable benefit, showing 2 or 3 weeks after the operation a definite improvement in cardiocirculatory function: liver enlargement and jugular venous engorgement were reduced and the size of the right heart and pulmonary artery significantly decreased (fig. 2). At the same time, the loud first sound and systolic murmur that were present before operation at the lower left sternal border or adjacent to it disappeared, and the findings became more clearly those of mitral stenosis, due to elimination of tricuspid insufficiency and increase in cardiac output. Electrocardiographic changes characterized by the disappearance of right ventricular hypertrophy, were noted only after 6 months or a year. Further observation demonstrated that the good results remained unchanged after 2 years.

In 3 others benefit was only partial, the evidence of tricuspid insufficiency being essentially unchanged, while the dyspnea and the other findings of mitral stenosis were reduced. In 2 of them an associated degree of tricuspid stenosis was detected by the surgeon and corrected by tricuspid valvulotomy, while in the third calcific fibrosis of the mitral cusps was found.

Seven other patients failed to demonstrate any improvement postoperatively, though severe mitral stenosis had been removed. In these subjects the most important finding at the operation was the rigidity and hardness of lungs, which hardly could be collapsed. In some of them, biopsy showed microscopic changes in the small pulmonary vessels, mainly in the arterioles, consisting in subintimal thickening with narrowing or obliteration of the lumen. Four of them developed congestive heart failure after the early postoperative course, with alternating periods

f slight improvement, and demonstrated some months later a more severe failure as compared with the preoperative observations. Finally, the remaining 3 died within 4 months after operation.

*Group II.* The 7 patients in whom a diagnosis of mitral regurgitation was made (of moderate degree in 5 and of a major degree in 2), showed no improvement. A few weeks after operation, the most striking clinical features were (1) a considerable increase in the apical systolic murmur, due to the mitral insufficiency, also in the 5 cases with a lesser degree of regurgitation; (2) left ventricular enlargement, present in all cases at the roentgen examination. The enlarged and dilated left ventricle was unable to carry on the increased work load determined by the change in hemodynamics. Thus, dyspnea and cardiac asthma were added to the preexistent tricuspid symptomatology. The electrocardiogram showed evidence of left ventricular strain in addition to the right or combined ventricular hypertrophy. One of these patients died of congestive heart failure 2 months after operation.

## Discussion

Tricuspid insufficiency associated with mitral disease, particularly mitral stenosis, raises a difficult problem as to the surgical correction of the latter.

This problem has been examined in 20 patients with advanced mitral disease, belonging to functional classes III and IV, in whom tricuspid insufficiency did not represent a transient episode of congestive heart failure, but was established for many years and did not respond to medical treatment. In 2 patients tricuspid insufficiency was associated with tricuspid stenosis. All patients were considered candidates for mitral commissurotomy on the basis of clinical findings of pure or predominant mitral stenosis.

Following operation, the course of the disease may be related to various clinical and pathophysiologic data, mainly: (1) type of mitral stenosis (pure or with insufficiency); (2) anatomic and functional conditions of pulmonary circulation; (3) type of tricuspid lesion (organic or functional); (4) myocardial function.

Table 3.—*Late Results after Commissurotomy in Patients with Mitral Disease Associated with Tricuspid Insufficiency*

| | Group I | | Group II | Total patients |
|---|---|---|---|---|
| | With pulmonary arteriopathy | Without pulmonary arteriopathy | | |
| Improved markedly | 1 | 2 | 0 | 3 |
| Improved slightly | 0 | 3 | 0 | 3 |
| Unchanged | 4 | 0 | 6 | 10 |
| Deaths | 3 | 0 | 1 | 4 |
| Total | 8 | 5 | 7 | 20 |

It is obvious that in the selection of patients for mitral commissurotomy, all these factors must be considered and possibly evaluated preoperatively. Some of them are difficult to assess on the basis of the preoperative findings; nevertheless, all are of paramount importance for the subsequent course of the disease.

*Type of Mitral Stenosis.* In all patients with mitral stenosis and insufficiency (group II), though the latter was moderate except in 2, the clinical improvement was slight or absent. All exhibited left ventricular failure, while the tricuspid insufficiency was unchanged.

Usually, moderate regurgitation associated with severe mitral stenosis was not reduced by operation and rather increased in many instances; however, moderate benefit was derived in most cases.[14] When, on the contrary the same condition occurred with complicating tricuspid insufficiency, little or no clinical improvement was observed. In fact, the persisting mitral regurgitation allowed only partial decrease in pulmonary hypertension, which was responsible for the right ventricular dilatation,[15] and, in turn, for the subsequent enlargement of the tricuspid ring

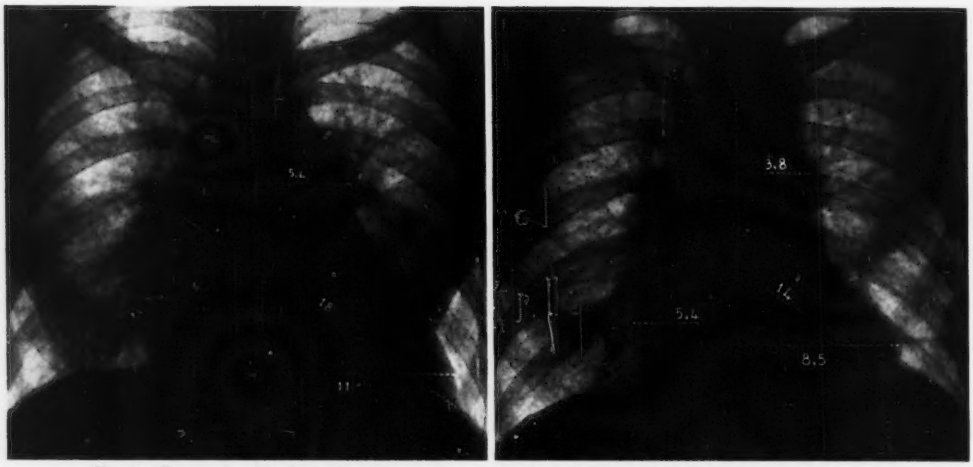

FIG. 2. Example of radiologic changes in a patient with pure mitral stenosis associated with tricuspid insufficiency. *Left.* Before operation. *Right.* One year after mitral commissurotomy. In this subject the clinical improvement was good.

and incompetence of the valve leaflets. Thus, mitral regurgitation, even of a lesser degree, seems to contraindicate the operation when tricuspid insufficiency is also present. Accordingly, the discovery of mitral insufficiency must be the subject of careful preoperative evaluation.

Better results were obtained in the group of patients (group I) with pure mitral stenosis. However, conditions mentioned below could interfere significantly in the postoperative course.

*Anatomic and Functional Changes in Pulmonary Circulation.* The 7 patients with pure mitral stenosis who had no improvement (3 of them died within 4 months after operation) demonstrated severe pulmonary arteriopathy.

Following the relief of valvular obstruction, the pulmonary resistances may fall only if functional in nature or if the anatomic vascular lesions are limited to muscular hypertrophy.[14] Therefore, an attempt to evaluate the anatomic condition of the pulmonary bed, should be made preoperatively. In our experience, the changes in pulmonary resistances after injection of reserpine during heart catheterization can be of great help:[16] if the pulmonary hypertension is mainly functional, injection of 2 mg. of this drug induces after 1 or 2 hours, a definite fall of pulmonary systolic pressure (10 to 70 mm. Hg), while systemic pressure remains unchanged (fig. 3). In 3 patients of this group, reserpine was injected during catheterization: 2 of them, who had a considerable fall in systolic pulmonary pressures, exhibited a good improvement after commissurotomy; on the contrary, the third who did not respond to the reserpine test, because of the presence of a pulmonary organic arteriopathy, showed poor postoperative results.

*Type of Tricuspid Lesion.* Of the 5 patients without pulmonary arteriopathy, 3 had partial, temporary relief from operation, but the symptoms due to tricuspid insufficiency relapsed as soon as they resumed their physical activity.

The lack of improvement in 2 cases was due to the existence of an organic lesion of the tricuspid valve: in fact a coexisting tricuspid stenosis was surgically corrected, probably resulting in a more severe insufficiency, as often occurs after operation of mitral stenosis associated with insufficiency. The other case concerned a man with calcific fibrosis of the mitral leaflets, which could not be satisfactorily fractured.

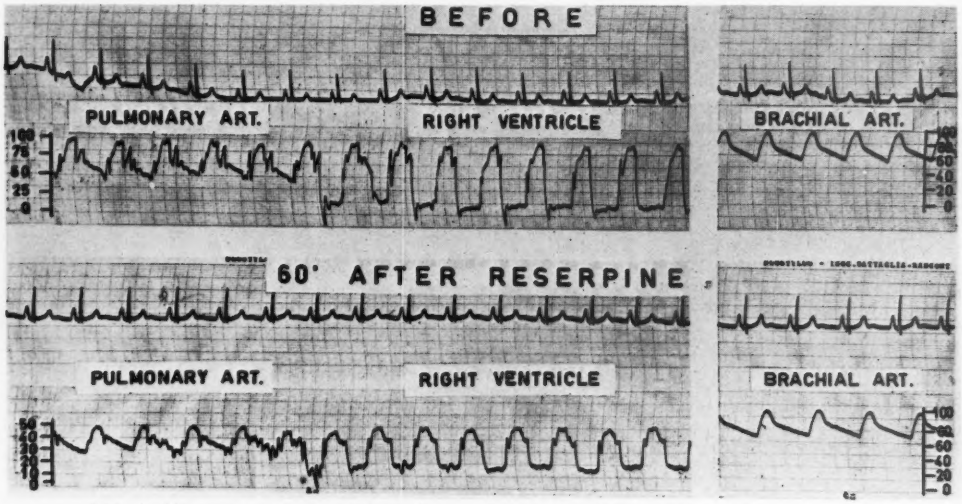


FIG. 3. Pressure tracings obtained from pulmonary artery, right ventricle, and brachial artery before and after injection of 2 mg. of reserpine through the catheter in a patient with pure mitral stenosis. Note the definite fall in systolic pulmonary and right ventricular pressure 60 minutes after injection (from 100 to 50 mm. Hg). Systemic pressure was unchanged. No significant modification was observed in the cardiac output and the heart rate.

The problem of differentiating organic from functional tricuspid insufficiency, is far from being solved.[1, 3, 6, 8] In the rare cases in which associated tricuspid stenosis is established by cardiac catheterization, the diagnosis of an organic lesion is certain. On the other hand, in the presence of pure insufficiency the functional lesion is always doubtful and only presumptive on the basis of a severe mitral obstruction leading to pulmonary arterial and right ventricular hypertension and eventually to right ventricular failure.

*Myocardial Function.* The myocardial response to the mechanical improvement brought about by mitral commissurotomy is an important determining factor in the subsequent course of the disease. It cannot completely be foreseen before operation, nevertheless it must be considered, not only in the presence of mitral regurgitation, but also when pure mitral stenosis is accompanied by roentgenologic evidence of enlargement of the left ventricle. The latter may have been damaged by a previous myocarditis.[17]

## SUMMARY AND CONCLUSIONS

Twenty patients, affected by mitral disease with tricuspid insufficiency and selected for mitral commissurotomy on the basis of clinical evidence of advanced heart disease, have been studied before and after surgery, in order to evaluate further modifications in cardiocirculatory function.

According to the type of mitral disease, 2 groups of patients have been distinguished: in 13, pure mitral stenosis was demonstrated, while in 7 mitral stenosis was associated with mitral insufficiency. An additional subdivision was made between subjects with moderate pulmonary hypertension and those with pulmonary arteriopathy among patients with pure mitral stenosis.

Good results were obtained in a few patients with severe pure mitral stenosis, moderate pulmonary hypertension, and functional tricuspid insufficiency.

Very poor improvement was observed in patients with mitral regurgitation, pulmonary arteriopathy, or organic tricuspid insufficiency. Two patients in this group died.

The myocardial response to the mechanical improvement brought about by mitral commissurotomy is an important factor in the subsequent course of the disease.

SUMMARIO IN INTERLINGUA

Vinti patientes, afficite de morbo mitral con insufficientia tricuspidal e seligite pro commissurotomia mitral super le base de provas de morbo cardiac de forma avantiate, esseva studiate ante e post le intervention chirurgic con le objectivo de evalutar modificationes additional in le functiones cardiocirculatori.

Secundo le typo de morbo mitral presente, 2 gruppos de patientes esseva distinguite: In 13, pur stenosis mitral esseva demonstrate, durante que le 7 alteres habeva stenosis mitral in association con insufficientia mitral. Le gruppo de patientes con pur stenosis mitral esseva subdividite additionalmente in subjectos con moderate grados de hypertension pulmonar e subjectos con arteriopathia pulmonar.

Bon resultatos esseva effectuate in plure patientes con grados sever de pur stenosis mitral con grados moderate de hypertension pulmonar, e con functional insufficientia tricuspid.

Pauchissimo satisfacente esseva le melioration observate in patientes con regurgitation mitral, arteriopathia pulmonar, o organic insufficientia tricuspidal. Duo mortes occurreva in iste gruppo.

Le responsa myocardial al melioration mechanic que esseva effectuate per le commissurotomia mitral es un factor inportante in le curso subsequente del morbo.

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# Nucleated Red Blood Cells in Congestive Heart Failure

*By* Abraham M. Frumin, M.D., Theodore H. Mendell, M.D., Solomon S. Mintz, M.D., Paul Novack, M.D., and Arthur T. Faulk, M.D.

NUCLEATED red cells may be discovered in the peripheral blood of patients with congestive heart failure. This phenomenon and its connotation of poor prognosis has not been generally recognized. Only a few reports, restricted primarily to the hematologic literature,[1-5] have stressed these findings. Because of the prognostic importance of peripheral nucleated red cells in congestive heart failure we are describing 5 cases with this finding (table 1) admitted to the Albert Einstein Medical Center, Southern Division, in a 6-year period. The previously reported cases are reviewed and analyzed.

## Report of Cases

*Case 1.* A 62-year-old white man, was admitted on December 2, 1951, with the chief complaint of cough, shortness of breath, and abdominal discomfort of 1 day's duration. A 1-year history of exertional dyspnea was obtained.

The blood pressure was 108/70, and the pulse was 190. The lips and nailbeds were cyanotic and there were signs of fluid retention in the lungs, liver, and legs The heart was enlarged to the anterior axillary line, the sounds were of poor quality, and a gallop rhythm was present. The patient, was given oxygen, digitalis, mercaptomerin, quinidine, penicillin, and meperidine. His condition deteriorated, anuria and jaundice developed, and he died in 3 days.

At autopsy the heart weighed 550 Gm. The chambers were markedly dilated and the left ventricle was hypertrophied. On gross and microscopic examination numerous old infarcts were seen in the left ventricular myocardium, and fresh soft infarcts were noted in the anterior apical and the posterior basal regions. The coronary vessels were severely sclerotic, and the left anterior descending and left circumflex arteries were occluded by old thrombi.

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*Case 2.* A 63-year-old white woman, was admitted on March 3, 1952, because of edema of the legs and chest pain on effort. She was apparently well until 1949, when she experienced an episode of precordial pain associated with dyspnea, which subsequently increased and was followed by pedal edema. A questionable history of rheumatic fever in childhood was elicited.

Physical examination revealed cyanosis, dyspnea, and icterus. The blood pressure was 170/88. The heart was enlarged. A diastolic thrill was felt in the aortic area, and loud aortic and mitral systolic murmurs and a soft mitral diastolic murmur were heard. The liver was enlarged and there was pitting edema of the lower extremities. A diagnosis of rheumatic disease with mitral stenosis and insufficiency and aortic stenosis was made. X-rays of the chest revealed fluid in both pleural cavities and enlargement of all cardiac chambers. The electrocardiograph showed right heart strain. The patient became progressively more decompensated in spite of usual cardiac therapy, jaundice increased, her blood pressure gradually fell, and she died in 8 days

Autopsy revealed atherosclerosis of the aorta and major branches. The lungs were edematous and there was advanced pulmonary atherosclerosis. The right ventricle was markedly hypertrophied and dilated and the right atrium was dilated. The left ventricle was minimally hypertrophied. There was no evidence of rheumatic valvular disease. The liver and spleen were congested and edematous and the kidneys exhibited focal pyelonephritis.

*Case 3.* A 77-year-old white man, was admitted on October 28, 1950, with a history of sudden onset of right upper quadrant abdominal pain and shortness of breath. There was no previous history of cardiac disease. The blood pressure was 150/80 and the pulse was 84 and irregular due to atrial fibrillation. There were rales in the lung bases bilaterally and the heart was enlarged to the left. The apical ventricular rate was 100. A grade-II aortic systolic murmur with radiation to the apex was heard. The liver was enlarged 5 cm. below the right costal border and the legs were edematous. A chest x-ray showed cardiomegaly with mild pulmonary congestion. The electrocar-

TABLE 1.—*Blood Studies in Five Cases*

| Case No. and date | 1 12/2 | 12/4 | 2 3/3 | 3/7 | 3/10 | 3 10/28 | 10/30 | 12/1 | 4 12.2 | 2/11 | 5* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Red blood cells (million per mm.³) | 4.1 | 5.95 | 5.95 | 5.31 | 5.21 | | | 3.56 | 4.39 | | |
| Hemoglobin (Gm. %) | 12.6 | | 17.2 | 16.0 | 17.6 | 15.0 | 17.6 | 11.7 | 13.3 | 15.1 | 17.6 |
| Hematocrit (%) | 39 | | | | | | 54 | | | | 52 |
| Mean corpuscular volume (μ) | 95 | | | | | | | | | | |
| Color index | 0.9 | | | | | | | | | | |
| Reticulocytes (%) | 8.4 | | | | | | 1.4 | | | | 5.8 |
| Nucleated red cells (per 100 white cells) | 2 | 1 | | | 3 | 2 | | 5 | | | 8 |
| White blood cells (per mm.³) | 12,900 | 16,900 | 11,600 | 26,450 | 13,600 | 10,200 | 8,900 | 24,280 | 13,000 | 14,450 | 17,650 |
| Polymorphonuclear cells (%) | 71 | 82 | 70 | 82 | 74 | 53 | 59 | 90 | 84 | 79 | 78 |
| Lymphocytes (%) | 17 | 17 | 30 | 18 | 22 | 29 | 33 | 3 | 13 | 18 | 13 |
| Eosinophilis (%) | | | | | | 1 | 2 | | | | |
| Monocytes (%) | | | | | 1 | 14 | 6 | 2 | 2 | 2 | 4 |
| Blast cells (%) | | | | | | 1 | 1 | | 1 | 1 | 3 |
| Platelets (per mm.³) | | | | | | | | | | | 160,000 |
| Myelocytes (%) | | | | | | | | | | | 1 |
| Metamyelocytes (%) | | | | | | | | | | | 1 |

*Serum bilirubin 2.6 mg. % (direct 1.6, indirect 1.0).

diograms revealed left ventricular strain but no signs of acute myocardial infarction. The patient was digitalized with good clinical response and was discharged in 4 days. The patient was readmitted on March 23, 1952, in acute pulmonary edema. He had suffered several episodes of acute pulmonary edema in the intervening 15 months. He died in 2 hours, despite therapy.

At autopsy there was moderate atherosclerosis of the aorta and major branches. There were bilateral pleural effusions, pulmonary edema and congestion, and areas of emphysema. The left ventricle was hypertrophied and all of the cardiac chambers were dilated. A thrombus was present in the left atrial appendage. Moderate coronary sclerosis and a fresh posterior myocardial infarction were noted. The spleen was congested and the liver showed congestion, fatty degeneration, and cirrhosis. The kidneys contained fresh and old infarcts.

*Case 4.* A 43-year-old white woman was admitted February 1, 1954, with dyspnea, hemoptysis, fever, and feeling of pressure in her chest of a few days' duration. There was no previous history of heart disease or rheumatic fever.

Physical examination revealed a thin, acutely ill patient with cyanotic lips and fingernails. The blood pressure was 120/70, and the temperature was 102 F. There were areas of dullness in the left base and in the right lung, and many rales throughout the chest. The heart was greatly enlarged. Atrial fibrillation was present, with a ventricular rate of almost 250 and a pulse rate of 160 per minute; murmurs were not heard. The liver was enlarged 4 cm. below the right costal margin. Chest x-rays showed cardiomegaly with straightening of the left heart border suggestive of mitral stenosis; there were multiple densities throughout both lungs due to possible pulmonary infarctions. Electrocardiograms revealed atrial fibrillation and right and left ventricular hypertrophy. Large amounts of digitalis were required to control the rapid ventricular rate. Anticoagulants, oxygen, mercurials, and antibiotics were also administered. The patient had a very stormy course with fever, cyanosis, and hemoptysis for a week. Rales were heard for 3 weeks. When the ventricular rate became slower a low-pitched, mid-to-late diastolic murmur was heard at the apex. After 4 weeks the cardiac rhythm was converted to

normal sinus rhythm with quinidine sulfate. The patient is well at present.

*Case 5.* A 72-year-old man, was admitted on November 15, 1957, because of cough, shortness of breath, and chest pain of recent onset. He had been treated with digitalis for 15 years because of hypertensive cardiovascular disease. The blood pressure was 120/100, and the pulse was 80. Bilateral basal rales, poor heart sounds, thready pulse, enlarged liver 6 cm. below the right costal margin, and slight bilateral pedal edema were present. The electrocardiogram showed a supraventricular tachycardia with intraventricular block. He was given lanatoside C, mercurials, oxygen, and narcotics, but he died the following day. The arterial oxygen saturation was 100 per cent (patient was receiving nasal oxygen at the time).

## Discussion

Our studies reemphasize the poor prognosis attached to the presence of nucleated red blood cells in the peripheral blood of patients with congestive heart failure. It will be noted that approximately 50 per cent of the patients died shortly after the discovery of the nucleated red cells. The cause of peripheral nucleated red cells in congestive failure is still controversial. The phenomenon was once thought to be due to anemia, but this theory was discarded when it was discovered in patients with normal red blood cell counts.

Groen and Godfreid[4] stated "decompensation alone does not seem to produce this phenomenon; it requires the presence of thrombi and/or infarcts in the lesser circulation. This is possibly why Waller et al.[3] did not find normoblasts in their cases of congestive failure, as they excluded all cases with complications from their study. The presence of normoblasts in the peripheral blood in heart failure thus seems to indicate that the condition is complicated by a mural thrombosis in the heart or pulmonary artery, or by pulmonary emboli, or by a combination of these conditions. Hence it is easily understood why peripheral normoblastosis is a sign of poor prognosis." Two of our patients showed no evidence of thrombi in the heart or pulmonary circulation. This observation seems to negate this latter hypothesis.

Two of our patients were studied extensively, hematologically. There was no evidence for a hemolytic process, i.e., absent spherocytes, a negative Coombs test, and normal erythropoietic activity of the marrow. Antemortem marrow aspirations revealed that erythropoiesis was normoblastic in nature and occurred in normal numbers with a normal erythroid/myeloid ratio. The origin of these normoblasts is still unexplained. They do not appear to originate from areas of extramedullary hematopoiesis such as the liver or spleen. No such foci have been described and none was found in the microscopic sections of livers and spleens of our patients. We must therefore assume them to originate in the marrow. The probable stimulus for their production was anoxemia resulting from cardiac disease. The importance of local (marrow) anoxemia should be emphasized. The nucleated red cells in the peripheral blood may be due to the premature or abnormal release from the marrow due to local anoxia.

It was formerly believed that normoblasts occurred most frequently in heart failure due to rheumatic heart disease. This has been subsequently shown to be untrue, as in the Cook County Hospital series[5] in which 2 patients had syphilis, 7 had cor pulmonale, and the rest were evenly divided among rheumatic, hypertensive, and coronary heart disease.

Reticulocytosis was undoubtedly of marrow origin and may have represented an attempt of the marrow to compensate for the arterial anoxemia. It should be remembered that reticulocytosis occurred in the presence of a normal red count and hemoglobin. Reticulocyte elevations of this magnitude, i.e., 5.8 and 8.4 per cent, are not found in the erythrocytoses due to arterial anoxemia. Some other cause should be ascribed to their presence in congestive failure. Possibly the acute onset of circulatory failure may be responsible for their presence.

The presence of jaundice in 3 of our patients is worthy of further comment. Although reported in previous cases, no hypothesis was

made to their possible etiology. The elevated direct serum bilirubin points to hepatocellular insufficiency rather than to a hemolytic process. Autopsy failed to reveal any significant gross or microscopic change in the liver; cardiac cirrhosis was not found. The bilirubinemia may therefore represent physiologic impairment of hepatic function resulting from arterial anoxemia or local anoxia.

Our findings and those reported in the literature reemphasize that the presence of nucleated red cells in the peripheral blood smear is of serious prognostic significance. It is difficult to draw specific conclusions because of the relatively few cases reported. Some of the cases had rheumatic heart disease with anemia, and subacute bacterial endocarditis was suspected. This anemia may have contributed to the production of nucleated red cells. In the patients with rheumatic heart disease with normal red cell and hemoglobin values, the nucleated red cells signified a poor prognosis with cardiac decompensation. The nucleated red cells may not be constant since they may temporarily disappear. Despite their disappearance these patients often succumbed within a short period of time.


## Summary

Five patients with congestive heart failure who had peripheral nucleated red cells are reported and the literature is reviewed.

We believe that bone marrow anoxia is the cause for the premature or abnormal release of nucleated red cells in congestive heart failure.

The presence of nucleated red cells in the peripheral blood of patients with congestive heart failure is suggestive of a poor prognosis.



## Acknowledgment

We wish to acknowledge the technical assistance of Miss Helen Gordon MT.ASCP.



## Summario in Interlingua

Es reportate le casos de cinque patientes con congestive disfallimento cardiac qui habeva erythrocytos nucleate in le circulation peripheric. Le litteratura es passate in revista.

Nos opina que anoxia in le medulla es le causa del liberation prematur o anormal de nucleate erythrocytos in congestive disfallimento cardiac.

Le presentia de erythrocytos nucleate in le sanguine peripheric de patientes con congestive disfallimento cardiac suggere un prognos pauco favorabile.


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# Postmyocardial Infarction Syndrome

*By* NELSON J. WEISER, M.D., MILTON KANTOR, M.D., AND HOLLIS K. RUSSELL, M.D.

A new syndrome that is likely to follow myocardial infarction has recently been described. The cardinal manifestations of this syndrome may easily be confused with other, more common sequels of myocardial infarction, including cardiac failure, further infarction of the myocardium, and pulmonary embolism. The result of such confusion may be inappropriate therapy. This paper reviews the recent literature and our own experience with this syndrome and discusses the therapeutic implications.

IN APRIL 1956 Dressler[1] first called attention to a syndrome that he had observed in patients following myocardial infarction and that he described under the rather nonspecific title of The Post Myocardial Infarction Syndrome. Subsequently, he and his co-workers[2, 3] reported additional cases, pointing out the importance of recognition of this syndrome and theorizing as to its possible pathogenesis. By January 1959, Dressler had personally observed 53 cases and estimated the incidence of this disorder at approximately 3 per cent of patients with acute myocardial infarction.[4]

The postmyocardial infarction syndrome is characterized by prolonged or recurrent fever, chest pain, and clinical and laboratory evidence of pericarditis, pleurisy, and pneumonitis. These abnormalities may occur alone or in combination, and all show a marked tendency to recurrence.

The fever may merge with the initial temperature elevation of the myocardial infarct, in which case the febrile period was unusually prolonged for infarction alone, or it may appear as a secondary rise from 1 to 8 weeks after the infarction. The temperature usually ranged between 101 and 102 F., persisted for approximately 1 week, and might be followed by a low-grade elevation to about 100 F. until the next bout of higher temperature occurred.

The chest pain usually appeared at the time the temperature became elevated, though in some instances it did not develop until the second or third febrile episode. Characteristically, the pain was pleuropericardial in type, but at times it closely resembled angina. In exceptional cases, pain was absent throughout the entire course of the illness.

Fibrinous pericarditis during the early course of acute myocardial infarction is fairly common, appearing on the second to fourth day when the evanescent pericardial rub denoting its presence is most frequently heard. Pericarditis in patients with the postinfarction syndrome differed in several important respects from that usually associated with infarction. A pericardial rub, which was found in 80 per cent of the cases, developed 3 to 24 days after the infarction; instead of being evanescent, it remained audible 7 to 10 days, occasionally recurred several weeks later. Moreover, although fibrinous pericarditis has not been uncommon with acute myocardial infarction, pericardial effusion has been so rare that it has become the subject of isolated case reports. In the cases studied by Dressler, almost half of the patients had pericardial effusion of sufficient degree to be diagnosable on serial x-ray studies. In several instances the pericardium was aspirated; the fluid was at times straw colored, and at other times was hemorrhagic even in the absence of anticoagulant therapy.

When pleural effusion appears during the course of myocardial infarction, it is usually attributed to either congestive heart failure

From the Veterans Administration Hospital, Wilkes-Barre, Pa.

or pulmonary infarction. In the cases described by Dressler, pleural involvement was very common, but in only 1 instance was cardiac failure coexistent, and none showed signs of pulmonary infarction. The effusion was minimal in some; in others it was a paramount change necessitating repeated paracentesis for relief. Like the pericardial effusion, the fluid obtained was at times straw colored, at other times intensely hemorrhagic.

Pneumonitis developed in approximately 25 per cent of the cases observed. In addition to cough, rales, and x-ray evidence of infiltration in one or both lungs, hemorrhagic expectoration also occurred. Hemorrhagic pneumonia after myocardial infarction has been observed in postmortem studies.[5] In none of the cases reported by Dressler were the pulmonary changes associated with thrombophlebitis, pulmonary embolism, or congestive heart failure.

Laboratory studies showed only a leukocytosis with a shift to the left and an increased sedimentation rate. In protracted cases, a moderate anemia and hypoproteinemia occasionally developed. The electrocardiogram, in addition to the signs of recent myocardial infarction, showed changes suggestive of pericarditis in about half of the cases. Such studies as cultures of blood and of the pericardial and pleural fluids, search for acid fast bacilli, tests for lupus erythematosus cells, cold agglutinins, heterophile antibodies, agglutinins for typhoid and brucella, and tuberculin tests were invariably negative.

As already mentioned, the course of the postmyocardial syndrome is characterized by its appearance within the first few weeks after the acute infarction, at which time it may be misinterpreted, and by the tendency to recurrences. A single episode of pleuropericarditis might last for 6 weeks, and there have been as many as 6 recurrences in some cases. The number of recurrences determines the duration of the illness, which may vary from a week to 6 months. In a few instances, relapses appeared as late as 2 years after the onset of illness but these late recurrences were seen only in patients treated with steroids for prolonged periods. The severity of the illness varied markedly. In some, the pericardial effusion was massive enough to endanger life by tamponade; in others, the syndrome had no effect on the patients' well being. In general, however, the prognosis is good if anticoagulant therapy is not administered because of an erroneous diagnosis. In 1 case at least, such therapy produced fatal cardiac tamponade.

Since the illness is usually self-limited, symptomatic therapy with salicylates, analgesics, or narcotics suffices for the majority of cases. Corticosteroids have been found to be almost specific, causing fever and chest pain to disappear within 24 hours. However, rebounds have been observed frequently after withdrawal, even as late as 2 years after the onset of treatment. Therefore, these drugs have been reserved for those patients with excruciating pain or with an unduly prolonged illness.

The cause of this syndrome remains unknown. Attempts to implicate an infectious process, bacterial or viral, have been unsuccessful. Antibiotics have had no effect on the clinical course. Anticoagulant drugs were suspected but cases have been found in which no such treatment was administered and the serous effusions have at times been straw colored.

The clinical features of the postmyocardial infarction syndrome resemble those also seen in the postcommissurotomy syndrome. It has been suggested by some that the latter actually represents a hypersensitivity reaction to antigens produced by the traumatized heart,[6] and the same type of mechanism may underly the postinfarction syndrome. Both clinically and experimentally, allergic pneumonitis and serositis have been observed and reported by Rich and Gregory,[7] Ellis and McKinlay,[8] and Harkavy.[9] It is, therefore, postulated by Dressler that the postmyocardial infarction syndrome may represent a

hypersensitivity reaction to autoantigens that result from necrosis of the myocardium. At times, the resultant inflammatory reaction may be hemorrhagic in character.

As is true with any diagnosis, that of the postmyocardial infarction syndrome can be made only if the condition is borne in mind. In the past, this complication was not recognized because its manifestations were erroneously attributed to other causes. When the fever and pericardial rub appeared early and were prolonged, it was considered that extensive infarction had taken place. Late appearance of fever, chest pain, and pericarditis was thought to represent additional myocardial infarction at that time. Pleuropericardial pain or pleural effusion, especially if associated with hemoptysis or hemorrhagic pleural fluid, was usually attributed to pulmonary infarction. Increase in the size of the heart shadow was explained as due to cardiac enlargement unless serial x-rays, which are usually not taken on patients with recent myocardial infarction, showed it to be due to pericardial effusion.

Recognition of this syndrome should not be difficult when it presents itself with the full-blown clinical picture. In its less classical form, when only the incomplete syndrome appears, it should be suspected, especially if there are recurrences. The diagnosis becomes difficult when fever is the only manifestation or when pneumonitis or pleural effusion is the dominant feature. It may readily be missed if the manifestations of the myocardial infarction are so mild and atypical as to remain unrecognized, and therefore not obviously related to an attack of pleuropericarditis and fever, which appears several weeks later.

## Case Reports

*Case 1.* The patient, a 43-year-old white man with angina pectoris for 1 month was admitted to the hospital on November 3, 1958, complaining of pain in the chest of 2 hours' duration. There were associated sweating, weakness, nausea and apprehension. His blood pressure was 150/100. The heart was not enlarged on percussion, the heart tones were quite distant, and there was a grade-I blowing systolic murmur at the base. The pedal pulses were present. The lungs were clear to percussion and auscultation and the remainder of the physical examination was normal.

The electrocardiograms showed the usual progressive changes of a posterolateral myocardial infarction (fig. 1). The chest x-ray on admission was normal. The serum transaminase was 148.

The patient was treated on the basis of a diagnosis of myocardial infarction with bed rest, morphine, and anticoagulants. He ran a somewhat atypical course. His temperature remained elevated for a total of 16 days and reached a maximum of 102 F. In addition, there was a loud pericardial friction rub first heard on the fifth hospital day and lasting until the sixteenth day of hospitalization. A bedside x-ray of the chest on the tenth hospital day showed considerable enlargement of the cardiac shadow as compared with the film taken on admission (fig. 2). It also showed evidence of fluid in the oblique fissure on the right. This enlargement persisted on serial x-rays until the thirtieth hospital day. There were no physical signs to suggest that the cardiac enlargement was on the basis of congestive failure, and congestive failure would also not have accounted for the prolonged fever or the prolonged pericardial friction rub. There was no evidence of tamponade at any time and the patient had no unusual symptoms after the fourth hospital day. Because of the evidence of more than the usual postinfarction pericarditis, anticoagulants were discontinued in order to avoid the risk of a hemopericardium. The heart size returned to normal, the friction rub disappeared, and the temperature became normal. The subsequent hospital course was entirely uneventful.

*Case 2.* This 52-year-old man was admitted to another hospital* on June 12, 1956, with symptoms and electrocardiographic evidence of an acute anterior wall myocardial infarction. His recovery was uneventful and the expected serial electrocardiographic changes occurred. He was readmitted 2 months later with a 3-week history of frequently recurring pain in the epigastrium radiating to the chest and both shoulders. The pain was worse on recumbency. On admission, a pericardial friction rub was heard and was continuously audible for 6 days. The pain lasted for 4 weeks. The temperature during this period was normal except for the first 2 days of hospitalization when the patient had an irregular temperature elevation to a maximum of 102 F. The sedimentation rate was elevated as was the white count. The chest x-ray on

*We wish to acknowledge the courtesy shown by the Wilkes-Barre General Hospital in permitting us to review the hospital records of this patient.

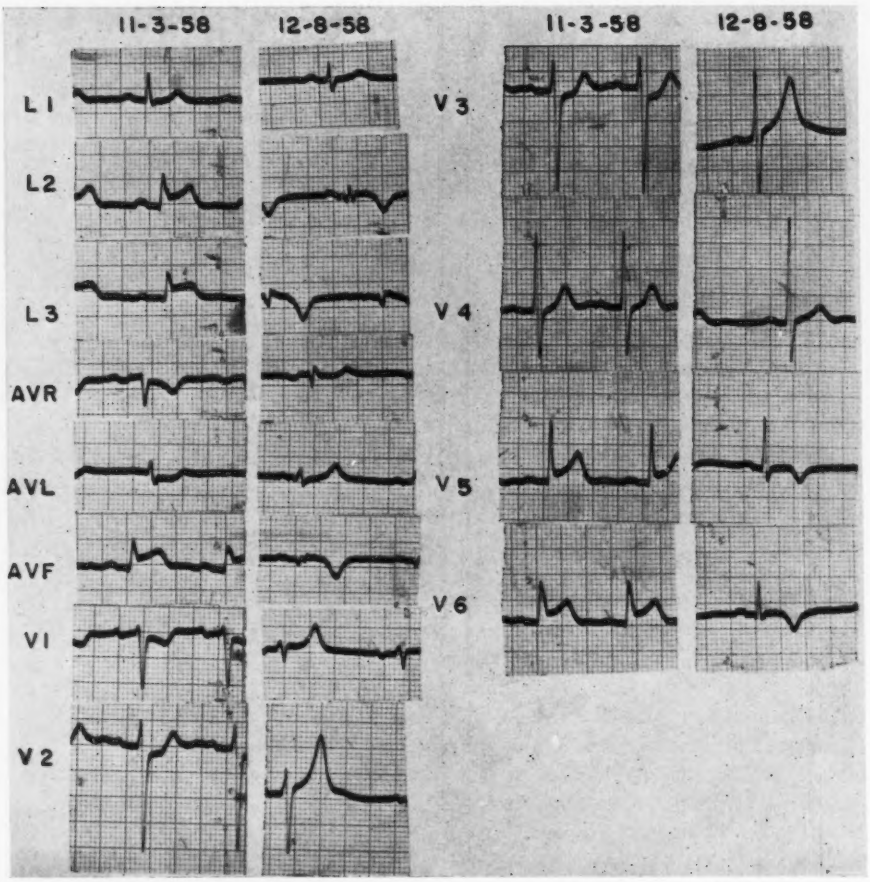


FIG. 1. Case 1. Electrocardiograms depicting the acute and healed stages of posterolateral wall infarction.

the seventh hospital day showed a small left pleural effusion, which was gone by the fourteenth hospital day. The heart size remained normal on both films. On admission, an electrocardiogram showed that the previously inverted T waves in the anterior chest leads had become upright. Serial tracings showed a return to the inverted T waves in all precordial leads followed by a return of the T waves to normal in $V_{1, 2}$, and $_3$. There was no ST-segment elevation at any time and no Q waves.

Two years later, he was again admitted to another hospital with a 5-day history of substernal pain radiating to the right arm and neck. This pain was not affected by nitroglycerin. A pericardial friction rub was heard from the eighth to the fifteenth day of this hospitalization. The temperature was essentially normal throughout this hospitalization and the serum transaminase was normal on 2 occasions. The chest x-ray was also normal. The electrocardiograms remained stable and showed essentially the residuals of a healed anterior wall myocardial infarction.

The patient was first admitted to the Wilkes-Barre Veterans Administration Hospital on November 22, 1958, complaining of episodes of rapid heart action and substernal pain. He stated that some episodes had been terminated by his private physician by means of pressure on the eyeballs but no electrocardiograms had been obtained at the time of these episodes. On admission, a sinus tachycardia had developed at a rate of 132, the blood pressure was normal, auscultation of the heart was negative, and the remainder of the physical examination was normal. There was no physical or laboratory evidence of thyrotoxicosis. The admission electrocardiogram was compatible with

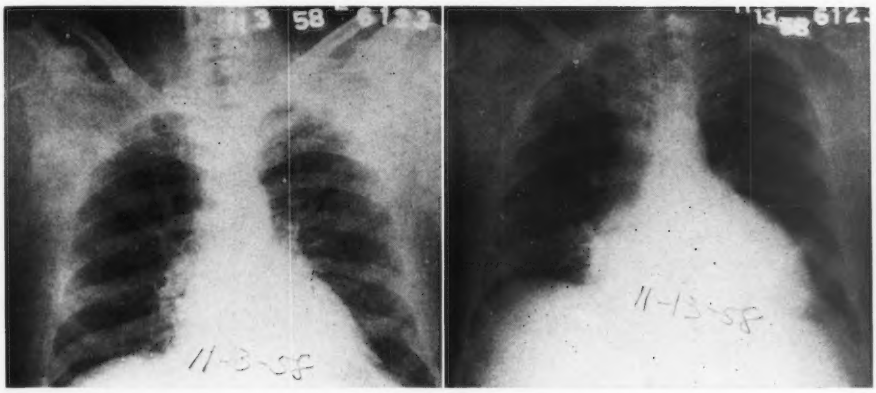

FIG. 2. Case 1. Comparative bedside chest x-rays showing the appearance of pericardial effusion 10 days after admission.

a healed anteroseptal myocardial infarction and serial electrocardiograms showed no significant changes. No episodes occurred during the patient's hospital stay to suggest paroxysmal tachycardia and it was concluded that the sinus tachycardia present on admission was on a functional basis. The patient responded to reserpine therapy, with symptomatic improvement and with a fall in the cardiac rate to normal.

*Comment.* This patient had a proved myocardial infarction 30 months prior to our first examination. From the records it appeared that 2 episodes of pericarditis had occurred 2 months and 2 years after the myocardial infarction. These were characterized by prolonged pericardial friction rubs without electrocardiographic evidence of fresh myocardial infarction. Fever and pleural effusion occurred in 1 episode. The transaminase was normal at the time of the second episode. On each occasion, the electrocardiogram was compatible with a healed myocardial infarction without evidence of further destruction of the heart muscle.

*Case 3.* This 50-year-old white man was admitted to the hospital on October 18, 1958, complaining of pain in the chest and hemoptysis, both of 12 hours' duration. Between 1955 and the summer of 1958 he had had 3 previous hospitalizations, each time for a fresh myocardial infarction. There was no previous history of hemoptysis or of chronic chest disease of any kind, no history of symptoms to suggest phlebitis; and no history of cardiac arrhythmia.

On admission, the blood pressure was 120/90. The heart sounds were distant and there were a few scattered rhonchi in the lungs. The electrocardiogram on admission showed, in addition to evidences of old infarction, generalized S-T depressions, suggesting coronary insufficiency. Subsequent tracings showed return to the pattern of healed infarction. A serum transaminase was normal.

The patient received oxygen, narcotics, and anticoagulant therapy with heparin and coumadin; adequate, but not excessive, anticoagulant levels were achieved. Nevertheless, the patient continued to cough up 2 to 3 ounces of grossly bloody sputum daily. Physical examination disclosed persistent rales at both bases, and digitalis was administered because it was difficult to differentiate left-sided decompensation from what was presumed to be multiple pulmonary emboli. Serial bedside chest films during this period disclosed gradually progressive, disseminated infiltrations in all lung fields (fig. 3). The final chest x-ray, obtained about 18 hours before the patient died, suggested pulmonary edema, but the patient's respiration was relatively easy at this time. During the third hospital day a distinct pericardial friction rub was heard, but none was heard subsequently. Moderate temperature elevation to 102 F. was present throughout the hospital course. On the seventh hospital day dyspnea rapidly increased and the patient expired within 2 hours, despite the usual therapy for left ventricular failure.

It was our clinical impression that the patient had had multiple pulmonary emboli from the right ventricle subsequent to previous infarction involving the septum, and that the coronary insufficiency or myocardial infarction had resulted from the secondary hypotension.

At postmortem examination the heart weighed 450 Gm. The pericardial sac contained 40 ml. of cloudy fluid and there were some fibrinous adhesions between the visceral and parietal pericardium, both anteriorly and posteriorly; these were

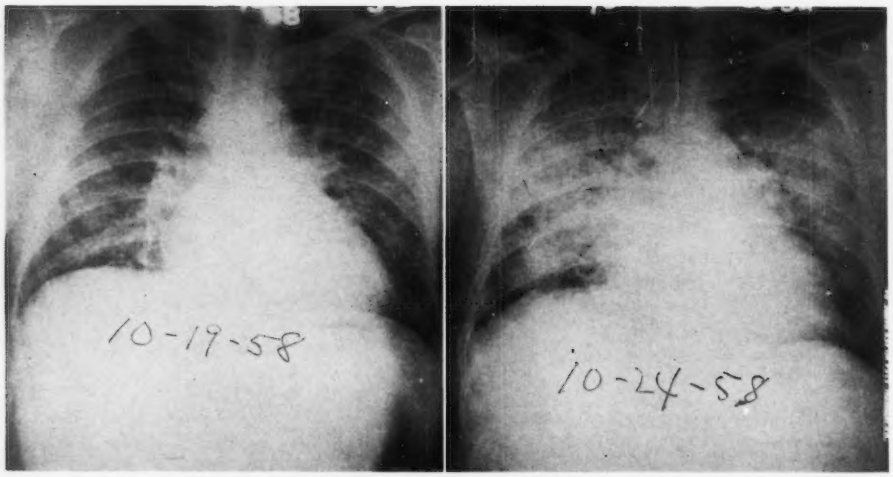


FIG. 3. Case 3. Serial bedside chest x-rays showing progressive bilateral pulmonary infiltrations due to hemorrhagic pneumonia.

broken without difficulty. The right coronary artery was occluded, 2.5 cm. from its origin by atherosclerotic plaques with hemorrhage beneath the intima and a thrombus in the lumen. A similar lesion occluded the left circumflex coronary artery 2 cm. from its origin. The valves on the left side of the heart showed moderate atherosclerotic thickening while those on the right side of the heart appeared normal. The left ventricular wall in its greatest thickness measured 1 cm. and the right ventricular wall measured 0.4 cm. The cardiac muscle showed aneurysmal dilatation in the region of the apex near the interventricular septum. In this area, the ventricular wall was thin, measuring only 3 mm., and intensely fibrotic. The cardiac muscle in other areas revealed a coarse pattern of fibrosis with no gross areas of acute necrosis of the cardiac muscle. No intramural thrombi were present.

The left lung weighed 775 Gm. and on palpation revealed patchy areas of consolidation involving most of the upper lobe and about half of the lower lobe. On section, the consolidated areas had a reddish brown appearance but were not granular and were thought to be resolving infarcts although the vessels of these areas failed to reveal evidence of thrombosis. The uninvolved portions of the lung showed some congestion and edema. The right lung weighed 1,000 Gm. and on palpation revealed nodular areas of consolidation involving primarily the upper and middle lobes and to a lesser degree the lower lobe. On section, the consolidated areas were rather ill defined and had a reddish brown color but were not granular. The pleural surface involved in the consolidated areas was not elevated or intensely congested. The bronchi of both lungs contained some blood-tinged sputum. The blood vessels appeared normal and showed no evidence of thrombosis.

On histologic examination, an epicarditis was seen corresponding with the fibrinous adhesions noted grossly. Sections of the coronary artery showed an organizing thrombus with some fresh thrombus engrafted upon the partially organized lesion. The adjacent myocardium revealed areas of necrosis infiltrated by neutrophilic leukocytes accompanied by an intense fibrinoblastic reaction. In addition, there were focal areas of subendocardial necrosis accompanied by acute inflammation.

The lungs showed fibrin plugs within the alveoli with areas of moderate infiltration by neutrophilic leukocytes. In many areas there was fibrinoid swelling and necrosis of the alveolar walls, and a hyaline membrane lined many of the alveoli. Fibrinoid changes were seen in the walls of some of the smaller arteries. There was proliferation of some of the septal cells forming a low cuboidal-cell lining with many of the alveoli containing a mononuclear exudate as well as many pigment-laden phagocytes. Many of the alveoli contained organizing fibrinous plugs containing desquamated alveolar lining cells. In many areas, the alveolar walls were thickened and infiltrated by mononuclear cells and occasionally by neutrophilic leukocytes. Occasional focal collections of lymphoid cells were noted (fig. 4).

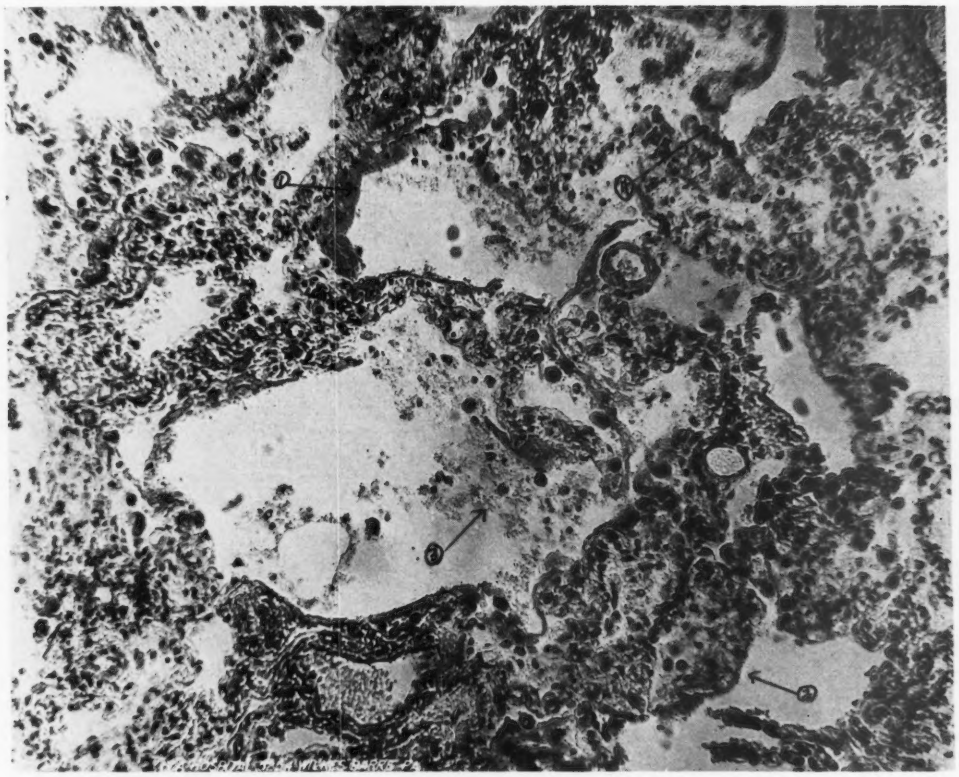

FIG. 4. Case 3. Microscopic picture of the lungs showing (*1*) hyaline membrane; (*2*) (*3*) desquamation of lining cells and accumulation of mononuclear exudate; (*4*) fibrinoid necrosis of the alveolar walls.

At the time of autopsy, it was thought that the pulmonary changes might represent organizing infarcts. Histologic study, however, failed to confirm this impression and no occlusion of the pulmonary vessels could be found. The microscopic picture resembled that seen in atypical or viral pneumonia, and was similar to the changes described by Geever et al.[5] as the atypical inflammatory reaction appearing in the lungs following acute myocardial infarction.

*Comment.* This patient had had at least 3 myocardial infarctions subsequent to 1955. His present episode began 1 week prior to death and was characterized by substernal pain, a pericardial friction rub, an electrocardiographic pattern of old myocardial infarction with superimposed coronary insufficiency, and profuse persistent hemoptysis. Physical and radiologic evidence suggested progressive, massive consolidation of both lungs; it was probably interstitial in its early stages, as suggested by the disproportion between radiologic consolidation and physical findings. Contrary to the expected behavior of pulmonary infarction, this lesion manifested itself by early hemoptysis and by progression in the face of anticoagulant therapy. The resemblance of this patient's x-rays to those of Dressler's patient with hemorrhagic bronchial pneumonia is striking.

Postmortem examination confirmed the absence of pulmonary emboli or of a source for pulmonary emboli. There were no postmortem findings in the pericardium that could be correlated with the pericardial friction rub that was heard early in the patient's course.

*Case 4.* This 64-year-old patient was first admitted to this hospital in 1954 with an anterior wall myocardial infarction. In late 1955 he was at another hospital with chest pain but no hemoptysis and was treated for pneumonia at both lung bases. The electrocardiograms at that time showed the residue of his myocardial infarction. In the spring of 1957, he was hospitalized with substernal

pain and hemoptysis. The hemoptysis began 48 hours after the onset of substernal pain. At that time, he had the progressive electrocardiographic changes of a fresh myocardial infarction as well as infiltration at the base of the right lung. The patient recovered without anticoagulant therapy, which was withheld because of a duodenal ulcer that had recently bled. The clinical diagnosis was myocardial infarction followed by pulmonary infarction. Six months later, he was readmitted with substernal pain and left pectoral pain, which was worse on inspiration. Hemoptysis, which had not been noted since his last admission, developed very shortly after the chest pain and totaled about 2 ounces in 3 days. On admission, the heart sounds were of poor quality and the lungs were clear on auscultation. There was no evidence of thrombophlebitis at any time. Serial electrocardiograms showed a third myocardial infarction but the chest x-ray revealed no pulmonary infiltration to correspond to the hemoptysis. The patient received anticoagulant therapy on this occasion and hemoptysis continued for a period of 1 week. The patient was readmitted to the hospital on December 15, 1958, with ulcer symptoms. There had been no clinical or electrocardiographic evidence of further myocardial infarction in the 14-month interval and no further hemoptysis.

*Comment.* Between 1954 and 1957, this patient had 3 myocardial infarctions. One year after the first infarction, he was treated for "pneumonia" without hemoptysis and without further evidence of myocardial infarction. The second and third episodes of myocardial infarction were accompanied by rather profuse and prolonged hemoptysis which, on the last occasion, began only a few hours after the onset of the symptoms of myocardial infarction. During the 5-year period of this patient's heart disease, hemoptysis had occurred only on these 2 occasions. It was the clinical impression, at the time of these 2 episodes, that this patient had had myocardial infarction and pulmonary infarction occurring almost simultaneously. It is our impression now, that this patient had myocardial infarction complicated by a hemorrhagic bronchopneumonia and that pulmonary infarction did not occur. The therapeutic implications, particularly with regard to anticoagulant therapy, are apparent.

## Discussion

Four patients have been presented with past histories of myocardial infarction who then developed unusual manifestations during the postinfarction period. These manifestations occurred as early as 5 days after the infarction and as late as 2 years after the infarction. They included prolonged or recurrent pericarditis in 2 cases and hemorrhagic pneumonia in 2 cases.

Therefore, there were 2 of Dressler's manifestations noted in our 4 patients. None of our patients had pleural effusion. Three of the 4 patients were febrile beyond the period of acute myocardial infarction and 1 had chest pain which could not be accounted for by infarction (case 2).

In treating myocardial infarction, it is standard practice to be aware of certain complications. Some of these (brief pericarditis without effusion, cardiac failure, and particularly pulmonary embolism) may mimic the manifestations described by Dressler. Failure to recognize this syndrome resulted in misdiagnosis in 2 of our 4 patients. A third patient was properly diagnosed as suffering from prolonged pericarditis with effusion (case 1), and a fourth suffered the major manifestations of his illness at another hospital.

Our errors and the resulting therapeutic implications may be summarized as follows:

Two of our patients developed hemoptysis and pulmonary infiltrations within a few hours after the substernal pain that signaled the onset of the infarction. One of these patients behaved in this fashion on at least 2 and perhaps on 3 occasions (case 4). In both patients we made a diagnosis of almost simultaneous pulmonary and myocardial infarction, attributing the pulmonary infarction to the previous history of arteriosclerotic heart disease and the myocardial infarction to the fall in blood pressure consequent to the pulmonary infarction. The explanation is labored enough, although supported by previous clinical experience; however, it was made even less tenable in 1 patient (case 3) by the clinical and radiologic evidence of progressive hemorrhagic consolidation of both lungs in the face of well-controlled anticoagulant therapy. It is fair to say that the unresponsiveness to anticoagulants was sufficient to call our attention to the true

tate of affairs in this patient and that in he other patient the coincidence of pulmonary and myocardial infarction might reasonably have been accepted once, but not wice. The therapeutic implications with regard to anticoagulant therapy are apparent. In addition, Dressler claimed success in reating this syndrome with steroids, which might have been tried in the patient who died of the progressive syndrome.

Two of our patients had pericarditis. The use of anticoagulants in the presence of severe and prolonged pericarditis is probably contraindicated, and it is particularly necessary to be prepared to tap the pericardium should severe tamponade result.

Pleural effusion is less a threat to the patient than are the other 2 complications, and therefore demands less therapy. It is necessary to be aware that the complication exists in order to avoid an erroneous diagnosis of cardiac failure or of pulmonary infarction. Once more the therapeutic implications are apparent.

We have nothing to add to Dressler's discussion of the possible etiology of these complications, or to his comments concerning the possible relation to similar manifestations following mitral commissurotomy, which also follow damage to heart muscle. If Dressler's concept of an allergic response to necrotic heart muscle is correct, then it is possible that the syndrome may occur in response to the gradual and progressive necrosis that occurs in some arteriosclerotic hearts without major infarction. This observation may or may not be related to the unexplained pleural effusions that are sometimes found in elderly and arteriosclerotic individuals who have never suffered acute myocardial infarctions. This is admittedly speculation and will require the observation of many such patients with this possibility in mind.


## Summary

Four patients have been described who had in common a history of myocardial infarction followed, after a varying interval, by unusual manifestations comprising prolonged or delayed pericarditis with or without effusion or hemorrhagic pneumonia without pulmonary infarction. The significance of these events is discussed, particularly with regard to potential misinterpretation as fresh myocardial infarction, pulmonary embolism, and cardiac failure. The therapeutic pitfalls involved in these errors in diagnosis are also discussed. Similar case material previously reported by Dressler is summarized with a discussion of the etiology, as yet unknown, of this syndrome. It is suggested that Dressler's original concept may require expansion to include patients with myocardial fibrosis on an arteriosclerotic basis but without acute infarction. In view of the ease with which we collected 4 cases of this syndrome after we became aware of it, we believe that these manifestations may not be uncommon.

## Summario in Interlingua

Es describite 4 patientes qui habeva in commun un historia de infarcimento myocardial, sequite—a varie intervallos—per un serie de manifestationes inusual consistente de prolongate o retardate pericarditis con o sin effusion o pneumonia hemorrhagic sin infarcimento pulmonar. Le signification de iste evenimentos es discutite, particularmente con respecto al risco de lor interpretation erronee como recurrentia de infarcimento myocardial, como embolismo pulmonar, e como disfallimento cardiac. Le periculo therapeutic inherente in tal errores diagnostic es etiam discutite. Simile observationes, previemente reportate per Dressler, es summarisate. Le question del non ancora cognoscite etiologia de iste syndrome es discutite. Es presentate le suggestion que le conception original de Dressler debe esser expandite de maniera que illo pote includer patientes con fibrosis myocardial a base arteriosclerotic e sin infarcimento. Viste le facto que nos habeva pauc difficultate a trovar 4 casos de iste syndrome post que nos habeva devenite conscie de su existentia, nos crede que le supradescribite manifestationes non es incommun.

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## SCIENCE AND LIFE

J. Arthur Thomson

British: professor of natural history, editor and author; 1861-1933

The old discouragement expressed in the saying that increase of knowledge is increase of sorrow has been replaced by a more robust confidence in what science may achieve in the control of life. The modern outlook is expressed in Herbert Spencer's pithy sentence: "Science is for life, not life for science," or in Comte's well-known saying: "Knowledge is foresight, and foresight is power."

Bacon had the idea clearly in mind when he wrote in *The Advancement of Learning:* "This is that which will indeed dignify and exalt knowledge if contemplation and action be more nearly and straitly conjoined and united together than they have been." And the passage ends by declaring that what is sought in science should be "a rich storehouse for the glory of the Creator and the relief of man's estate." But what is distinctively modern is the ideal of bringing the light of science to bear on man's problems all along the line, on health of mind as well as of body, on education as well as on agriculture, on ethical development as well as on the more economical exploitation and usage of natural resources, on eugenics as well as on eutopias. Just as many ills that the flesh is heir to are met no longer with folded hands but by confident therapeutics, so over a wide range there is a promiseful application of all kinds of science to the amelioration of the conditions of human life. Great stores of wealth are awaiting the scientific "Open Sesame"; a great heightening of the standard of health will be attainable in a few generations if men of good-will take science as their torch. But wealth and health are the pre-conditions of true progress, which means a fuller embodiment of the true, the beautiful, and the good in lives which are increasingly a satisfaction in themselves.—*The Outline of Science,* Vol. 4, p. 1165. From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

# Effects of Infusion of Acetylcholine on Pulmonary Vascular Resistance in Patients with Pulmonary Hypertension and Congenital Heart Disease

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Survival following surgical correction of congenital cardiovascular defects is unlikely if pulmonary hypertension cannot be decreased significantly. Infusions of acetylcholine decreased pulmonary vascular resistance in 6 of 11 patients having pulmonary hypertension associated with atrial or ventricular septal defects. When the acetylcholine was combined with the breathing of oxygen, resistance decreased further. These findings are consistent with the theory that, at some stage, the pulmonary hypertension in cases of congenital heart disease is maintained at least in part by vasoconstriction and therefore is potentially reversible.

MANY patients with pulmonary hypertension associated with intracardiac or great vessel defects have increased resistance to blood flow through the pulmonary vascular bed.[1-6] It is important to know how much, if any, of this increased resistance is due to active vasoconstriction. If vasoconstriction can play an important role, then its assessment may be helpful in evaluating the condition of patients with pulmonary hypertension before surgical correction of the defects, and in understanding the way in which the constriction is induced and maintained.

Acetylcholine, which causes local vasodilatation when injected intra-arterially into systemic vessels[7] has been used recently in the study of the pulmonary circulation.[8-10] Rapid inactivation of this substance in the circulating blood makes possible its injection into the pulmonary artery in sufficient concentration to affect the pulmonary vessels without altering the hemodynamics of the systemic circulation. Harris[8] found that sudden single injections of acetylcholine into the pulmonary artery of patients with pulmonary hypertension, some of whom had congenital heart disease, could produce a transient fall in the pulmonary artery pressure. He suggested that this fall resulted from a decrease in pulmonary vascular resistance.

We have extended the technic by the use of constant-rate infusions of acetylcholine in an attempt to obtain the data necessary to calculate the changes in pulmonary vascular resistance. These observations were made first with the patients breathing air and repeated with the patients breathing oxygen; the latter was done because oxygen breathing alone can lower pulmonary resistance.[11-13]

The results show that the elevated pulmonary vascular resistance may be decreased during administration of acetylcholine, whether the patient is breathing air or oxygen.

## METHODS

Eleven patients, aged 8 to 51 years, with pulmonary hypertension were studied. Six had an atrial septal defect, 4 a ventricular septal defect, and 1 an atrial and a ventricular septal defect (table 1). The usual technic was as follows: A 7-F. catheter of the Lehman type with a bird's-eye tip

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TABLE 1.—*Results of Continuous Infusions into Main Pulmonary Arteries*

| Case | Age (yr.) & sex | Diagnosis* | When measurements were made† | Acetylcholine (mg./min.)‡ | | Pulmonary artery: Mean pressure (mm. Hg) | | Pulmonary artery: Flow (L./min.) | | Total pulmonary resistance (dynes sec. cm.$^{-5}$) | | Systemic arterial $O_2$ saturation (% (breathing air |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Air§ | Oxygen§ | Air§ | Oxygen§ | Air§ | Oxygen§ | Air§ | Oxygen§ | |
| 1 | 29M | ASD | Before | | | 39 | 38 | 7.0 | 9.2 | 445 | 330 | 96.0 |
| | | | During | 8.0 | 8.0 | 35 | 35 | 8.0 | 11.7 | 350 | 240 | 95.0 |
| 2 | 31F | ASD | Before | | | 60 | 60 | 4.0 | 5.3 | 1200 | 905 | 92.0 |
| | | | During | 2.0 | 8.0 | 53 | 56 | 4.5 | 5.9 | 940 | 755 | 92.0 |
| 3 | 35F | ASD | Before | | | 60 | 58 | 4.1 | 6.0 | 1170 | 775 | 96.0 |
| | | | During | 4.0 | 4.0 | 59 | 58 | 5.1 | 7.4 | 925 | 625 | 96.0 |
| 4 | 35F | ASD | Before | | | 35 | 27 | 8.0 | 10.4 | 350 | 210 | 96.0 |
| | | | During | 4.0 | 4.0 | 25 | 19 | 9.1 | 10.9 | 220 | 140 | 96.0 |
| 5 | 40M | ASD | Before | | | 66 | 68 | 3.2 | 4.1 | 1650 | 1325 | 92.0 |
| | | | During | 24.0 | 12.0 | 60 | 65 | 3.4 | 4.3 | 1410 | 1210 | 87.5 |
| 6 | 51F | ASD | Before | | — | 45 | — | 4.8 | — | 750 | — | 89.0 |
| | | | During | 2.0 | | 26 | — | 5.7 | — | 365 | — | 87.0 |
| 7 | 8M | VSD | Before | | | 69 | 67 | 3.4 | 4.3 | 1620 | 1250 | 94.6 |
| | | | During | 0.25 | 0.25 | 32 | 31 | 5.0 | 6.0 | 510 | 420 | 93.2 |
| 8 | 15F | VSD | Before | | — | 72 | 75 | 3.6 | 3.4 | 1565 | 1765 | 87.0 |
| | | | During | 4.0 | | 75 | — | 3.4 | — | 1765 | — | 87.0 |
| 9 | 43F | VSD | Before | | | 93 | 88 | 4.0 | 7.5 | 1860 | 940 | 92.5 |
| | | | During | 6.0 | 3.0 | 88 | 80 | 4.4 | 9.1 | 1600 | 705 | 92.5 |
| 10 | 49M | VSD | Before | | | 86 | 86 | 3.6 | 4.9 | 1910 | 1400 | 90.0 |
| | | | During | 6.0 | 12.0 | 83 | 83 | 3.9 | 5.3 | 1700 | 1250 | 90.7 |
| 11 | 25M | ASD | Before | | | 77 | 75 | 5.3 | 5.5 | 1160 | 1090 | — |
| | | & VSD | During | — | 4.0 | — | 75 | — | 5.5 | — | 1090 | — |

*ASD, atrial septal defect; VSD, ventricular septal defect.

†Before and during refer to measurements made just before and during infusion of acetylcholine.

‡Dose of acetylcholine that produced maximal response while patient was breathing air or oxygen.

§Measurements made when the patient was breathing air and 99.6 per cent oxygen respectively.

was used. This catheter, which has an internal diameter of 1.4 mm., was attached by a special adapter to a 3-way stopcock which allowed interchangeable connection of the catheter to a strain-gage manometer for recording pressure and to a cuvette oximeter for continuous recording of the oxygen saturation. The special adapter which was interposed between the catheter and the stopcock had a side arm through which a plastic catheter tubing of small size (outside diameter 0.6 mm., inside diameter, 0.3 mm.) was inserted via a packing nut and a close-fitting gasket.[14] This inner tubing was advanced so that its distal tip lay just within the intracardiac end of the catheter to be inserted into the right heart. An airtight seal between the shaft of this small plastic tube and the side arm of the adapter was accomplished by tightening the packing nut onto the side arm of the adapter. This airtight seal made possible the recording of pressure or withdrawal of blood samples via the lumen remaining between the inner plastic tubing and the internal surface of the lumen of the conventional right heart catheter.

The 7-F. catheter containing the long plastic tube was introduced, usually via a percutaneous puncture of an antecubital vein with a special thin-walled, 12-gage needle. After the tip of the catheter had been manipulated into the right heart and positioned in the pulmonary artery, the packing nut securing the inner plastic tube was loosened and the tube was advanced so that its tip was 2 to 3 cm. distal to the tip of the right heart catheter. The packing nut was again tightened securing the inner tubing in this position. It was now possible to inject acetylcholine via the inner plastic tubing while simultaneously recording pressure or oxygen saturation of the blood via the outer catheter. Acetylcholine in

graded doses was infused through the plastic tubing with a pneumatic stainless steel syringe described previously.[15] Acetylcholine was injected at a constant rate for 1 to 2 minutes. The Lehman catheter was used to monitor alternately the pulmonary artery pressure by a strain-gage manometer and the oxygen saturation by a cuvette oximeter before, during, and after the infusion. The aim was to infuse the acetylcholine into both pulmonary arteries, hence the tip of the Lehman catheter was positioned just beyond the pulmonary valve.

Radial artery pressure was measured continuously by a needle in the artery connected to a strain-gage manometer, and an absolute-recording ear oximeter was used to monitor the systemic arterial oxygen saturation. Tidal volume and oxygen consumption before, during, and after the infusion were monitored by a closed circuit spirometer. An electrocardiogram of standard lead I was recorded throughout.

In 3 cases in which the 7-F. catheter was too large for the vein, 2 5-F. catheters of Lehman type were used and inserted into the pulmonary artery. One was used for the injection and the other was connected via a 2-way stopcock to a strain-gage manometer and cuvette oximeter for monitoring pressure and oxygen saturation. In some patients the oxygen saturation of radial arterial blood was determined continuously during the infusion by a cuvette oximeter.

The procedure was usually carried out first with the patient breathing air and then repeated with the patient breathing 99.6 per cent oxygen. No measurements were made until the patient had been breathing oxygen for at least 5 minutes. As a safety measure and in order to be certain that an effective concentration of acetylcholine reached the small pulmonary vessels, a dose-response curve was made for each patient. In patients who showed a significant fall in pulmonary artery pressure, or a rise in pulmonary artery oxygen content, or both, without systemic or respiratory effects, no attempt was made to increase the dose to a point where changes in heart rate, systemic blood pressure, tidal volume, or respiratory rate were produced. If no effect was observed on the pulmonary circulation, the dose was increased until slight systemic effects were noted. The usual dose of acetylcholine chloride was 2 to 4 mg. per minute dissolved in isotonic saline solution, but in 1 patient 24 mg. was given per minute. The volume infused did not exceed 24 ml. per minute.

The total pulmonary resistance, expressed in dynes second cm.$^{-5}$, was calculated from the ratio: (pulmonary artery mean pressure [mm. Hg] × 1332) divided by (pulmonary flow [ml. per second]). For calculation of pulmonary blood flow the oxygen content of blood in the pulmonary artery was obtained from the oxygen capacity estimated by the method of Sendroy[16] as modified by Roughton, Darling, and Root[17] and the percentage saturation of blood in the pulmonary artery was determined by the cuvette oximeter.

All except 1 patient (case 7, table 1) had a veno-arterial shunt, the magnitude of which was estimated from the indicator-dilution curve recorded just before the infusion of acetylcholine by a method described elsewhere.[18] The magnitude of the shunt ranged from 5 to 32 per cent. For this reason the arterial oxygen content could not be used to indicate oxygen content of the blood in the pulmonary vein. As our patients except patient 6 (table 1) had no evidence of pulmonary disease, the oxygen content of pulmonary vein blood was assumed to equal 98 per cent of the oxygen capacity plus 0.3 vol. per cent to allow for physically dissolved oxygen when the patient was breathing air, and to equal the oxygen capacity plus 1.9 vol. per cent when the patient was breathing 99.6 per cent oxygen.

For patient 6 (table 1), who had pulmonary disease, the oxygen content of pulmonary vein blood was estimated as follows. The magnitude of the veno-arterial shunt was estimated from an indicator-dilution curve[18] and since the oxygen saturation of mixed venous blood and the oxygen saturation of blood in the radial artery were known, it was possible to calculate the oxygen content of blood in the pulmonary vein.[19]

## Results

*Pulmonary Hypertension Associated with Atrial Septal Defect.* During administration of acetylcholine to a 35-year-old woman (case 4, table 1) who had an atrial septal defect and pulmonary hypertension, the pulmonary artery pressure fell promptly from 66/18 to 52/12 mm. Hg and a small but concomitant rise occurred in the oxygen saturation of the right ventricular blood (fig. 1). The heart rate increased from 78 to 84 beats per minute, the systemic pressure fell by 5 to 7 mm. Hg, and the respiration slowed from 15 to 12 per minute. After the infusion was stopped, the pulmonary artery pressure returned slowly to the control level, a finding previously reported by Harris.[8] The total pulmonary resistance dropped from 350 to 220 dynes sec. cm.$^{-5}$ The resistance when the patient was breathing oxygen was 210

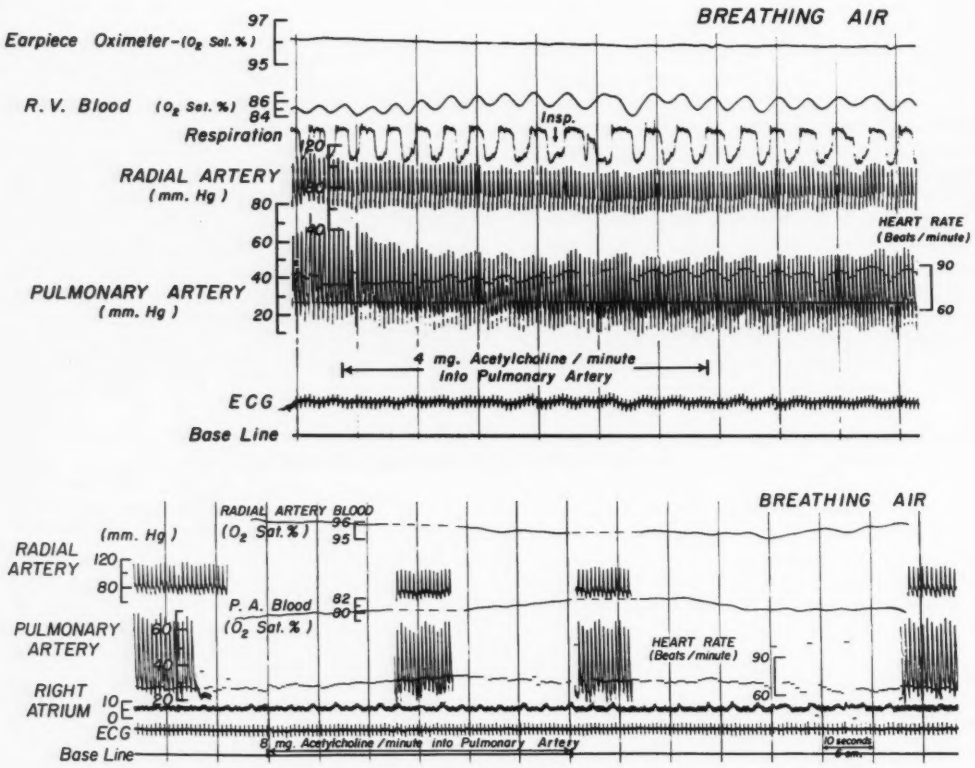


FIG. 1 *Top.* Case 4. Effects of a continuous infusion of acetylcholine into the pulmonary artery of a 35-year-old woman with an atrial septal defect and pulmonary hypertension while breathing air. The prompt fall in pulmonary artery pressure associated with a rise in oxygen saturation of right ventricular blood on administration of acetylcholine should be noted. The vertical time lines are at intervals of 10 seconds and were 5 cm. apart before photographic reduction of the record.

FIG. 2 *Bottom.* Case 1. Effects of a continuous infusion of acetylcholine into the pulmonary artery of a 29-year-old man with an atrial septal defect and pulmonary hypertension while breathing air. A slight fall in oxygen saturation of the radial artery blood associated with a rise in the oxygen saturation of pulmonary artery blood occurred.

and this fell to 140 when acetylcholine was administered.

The response observed in a 29-year-old man (case 1, table 1) with an atrial septal defect and pulmonary artery pressure of 65/26 mm. Hg is shown in figure 2. During the infusion of 8 mg. of acetylcholine per minute into the pulmonary artery with the patient breathing air, the oxygen saturation in the pulmonary artery blood rose from 79.5 to 82 per cent. This was accompanied by a change in oxygen saturation of radial artery blood from 96 to 95 per cent. Only a slight fall in pulmonary artery pressure, a decrease of about 10 mm. Hg in radial artery pressure, and little change in heart rate occurred. The total pulmonary resistance on infusion of acetylcholine fell from 445 to 350 dynes sec. cm.$^{-5}$ while the patient was breathing air and from 330 to 240 while he was breathing oxygen.

The results for all the patients are summarized in table 1 and in figure 4. All 6 of the patients with atrial septal defects showed

decreases in pulmonary resistance on administration of acetylcholine. If the pulmonary resistance when the patient is breathing air is taken as 100 per cent, the pulmonary resistance in the 5 patients for whom a complete set of data was obtained decreased 23 per cent with infusion of acetylcholine alone, 39 per cent on breathing oxygen, and 43 per cent on breathing oxygen and receiving acetylcholine.

*Pulmonary Hypertension Associated with Ventricular Septal Defect.* The most dramatic response to acetylcholine that was obtained in any of the patients studied is illustrated by figure 3. The patient, an 8-year-old boy (case 7), had a ventricular septal defect. The pressures in the pulmonary artery and femoral artery of this patient were similar at the start of the procedure. On infusion of acetylcholine while the patient was breathing air, the pulmonary artery pressure fell to less than half its previous value and the oxygen saturation in the pulmonary artery blood rose from 75 to 83. The calculated pulmonary resistance fell from 1620 to 510 dynes sec. cm.$^{-5}$ Breathing oxygen had only a minimal effect with a change in resistance from 1620 to 1250 dynes sec. cm.$^{-5}$ The high resistance to flow through the pulmonary vessels in this boy permitted the equalization of pressures in the 2 ventricles. When this resistance had been markedly decreased by the acetylcholine, a large pressure gradient developed between the ventricles, and the defect itself now constituted a major part of the resistance limiting the arteriovenous shunt. This patient also (fig. 3) showed a slight but definite decrease in systemic arterial oxygen saturation similar to that shown in figure 2.

Acetylcholine had little effect in reducing the pulmonary resistance in a 43-year-old woman (case 9, table 1) with a ventricular septal defect and pulmonary artery pressure of 139 mm. Hg systolic and 70 mm. Hg diastolic. Pulmonary resistance decreased from 860 to 1600 dynes sec. cm.$^{-5}$ while the patient was breathing air and receiving acetylcholine, a change of questionable significance; yet when she was breathing oxygen without acetylcholine, the resistance decreased to 940, a change of nearly 50 per cent. When she received acetylcholine during oxygen breathing, a small further decrease in resistance occurred (940 to 705). In this patient, therefore, oxygen and not acetylcholine had the greater effect on the pulmonary vessels.

Of the 4 patients in the series with ventricular septal defects only 1 (case 8) did not respond to either oxygen or acetylcholine. For the remainder the average percentage decrease in resistance with acetylcholine while breathing air was 31 per cent, while breathing oxygen, 33 per cent, and while breathing oxygen and receiving acetylcholine, 57 per cent. Pulmonary resistance while breathing air is taken as 100 per cent.

## Discussion

Various assumptions have been made in the calculation of the pulmonary vascular resistance. First, there was no direct measurement of the oxygen content of the blood in the pulmonary veins. On 4 occasions the oxygen saturation of the systemic arterial blood decreased slightly during infusion of acetylcholine when the patients were breathing air (table 1); this occurred at a time when the oxygen saturation of pulmonary artery blood was rising (figs. 2 and 3). This decrease in oxygen saturation, though small, may be significant, but we cannot say with certainty whether it was due to an increase in veno-arterial shunt or a decrease in oxygen content of pulmonary vein blood. Paul Wood[20] has noted that acetylcholine sharply lowered the arterial oxygen saturation in a case of cor pulmonale, and we have seen a similar decrease in a patient who had persistent pulmonary hypertension following apparently complete closure of a ventricular septal defect. Whatever the correct explanation, the assumptions made for the oxygen content of pulmonary vein blood in the present study would not overestimate the pulmonary blood flow during infusion with acetylcholine.

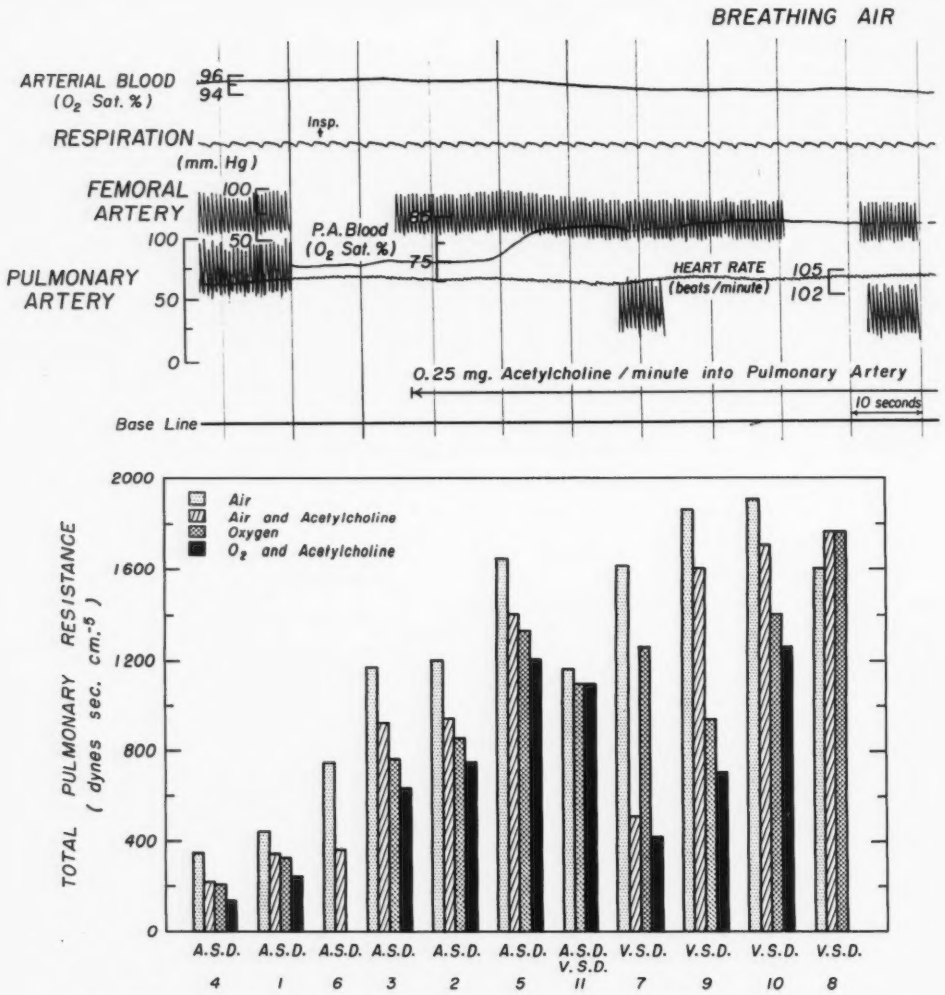


FIG. 3 *Top.* Case 7. Effects of a continuous infusion of acetylcholine into the pulmonary artery of an 8-year-old boy with ventricular septal defect and pulmonary hypertension while breathing air. The pulmonary artery pressure decreased markedly and the oxygen saturation of pulmonary artery blood increased.

FIG. 4. *Bottom.* Pulmonary resistance in the 11 patients with pulmonary hypertension. *ASD,* atrial septal defect; *VSD,* ventricular septal defect.

The pulmonary artery wedge pressure which presumably reflects mean left atrial pressure with acceptable accuracy[21–24] was measured in all patients before administration of acetylcholine and was within normal limits. In 2 patients with atrial septal defects (cases 1 and 11, table 1) the right atrial pressure was monitored continuously and did not change; hence it is unlikely that the left atrial pressure fell. If one accepts then that the left atrial pressure did not fall during infusion, one can conclude that the changes in total pulmonary resistance as determined by the method employed reflect actual changes in pulmonary vascular resistance.

Another assumption made in these studies is that the rise in oxygen saturation of the pulmonary artery blood indicates an in-

rease in pulmonary blood flow. Such a rise n pulmonary artery saturation with no rise n flow would reduce oxygen absorption by he lungs. Spirometric tracings did not indiate a decrease in oxygen absorption during njection of acetylcholine, but one must remember that an increase in functional residal capacity will simulate oxygen absorpion. Inspection of continuous tracings taken efore, during and after infusion did not how any evidence of changing functional esidual capacity. In 7 patients, there was a all in pulmonary artery pressure and a ise in oxygen saturation of the pulmonary rtery blood during infusion of acetylchoine. If these findings are to be explained as ndicating other than a decrease in the resistance of flow in the pulmonary vascular bed, one must assume that the systemic venous return decreased. The relative constancy of arterial pressure and pulse rate makes it unlikely that the infusion affected the left ventricle or systemic arterial bed; hence, such a decrease in systemic venous return if it did occur would have to be due to venous pooling or the combination of an increase in systemic vascular resistance and a decrease in stroke volume. It is concluded that these are unlikely explanations for the findings presented and that, in fact, a decrease in resistance to flow through the pulmonary vascular bed is caused by infusion of acetylcholine.

The assumptions made in concluding that oxygen also causes a decrease in resistance are similar to those described by Marshall and associates.[25]

Paul Wood[26] stated that both acetylcholine and oxygen fail to lower the pulmonary vascular resistance in cases of Eisenmenger's syndrome in adults and in children more than 5 years old. Any difference between our findings and his can be explained in various ways: 1. It may be that all the patients in Wood's series resembled the 2 in our series who did not respond (cases 8 and 11). 2. If only the pulmonary artery pressure and the oxygen saturation of systemic arterial blood were measured during a sudden single injection of acetylcholine in a patient with a large ventricular septal defect, the evidence for a drop in resistance may be missed as it would consist chiefly of a change in oxygen content of pulmonary artery blood since systolic pressures in the 2 sides of the heart would be equalized via the large defect. The fact that the oxygen saturation of systemic arterial blood does not change may well be the resultant of a decrease in pulmonary vein oxygen saturation offset by a diminution in a venoarterial shunt. Similarly, in a patient with an atrial septal defect a decrease in pulmonary vascular resistance could be missed if the increased flow through the pulmonary vessels consequent to the infusion of acetylcholine maintained the pressure in the pulmonary artery at its previous level, the principal change being a rise in oxygen content in the pulmonary artery blood.

One additional problem in interpretation merits emphasis. Acetylcholine is a potent bronchoconstrictor, and we have found that doses of acetylcholine which cause bronchoconstriction actually can increase a venoarterial shunt as measured by indicator-dilution curves. It is important, therefore, to monitor the pattern of respiration during infusion. Indeed, such bronchoconstriction might explain the rise in pulmonary artery pressure reported in anesthetized dogs[27] and in newborn infants.[28]

It is difficult to state the magnitude of change in calculated pulmonary resistance that should be accepted as demonstrating an increase in caliber of the pulmonary vessels. If the pulmonary resistance when the patients were breathing air is taken as 100 per cent, a fall in resistance of more than 45 per cent occurred in 4 patients with an atrial and in 2 with a ventricular septal defect when they were receiving acetylcholine, either when they were breathing air or oxygen. We believe that a fall of this magnitude represents a dilatation of vessels in the lung.

In the dosages used, neither inhalation of oxygen nor the infusion of acetylcholine produces a maximal reduction of pulmonary vascular resistance. Indeed, one agent may

be effective and the other ineffective in any given case.

Our results indicate that active vasoconstriction is important in maintaining the increased pulmonary resistance in many patients with congenital heart disease. This constriction is present both in patients with ventricular septal defects in whom the smooth muscle in the pulmonary vessels may have persisted from birth and in patients with atrial septal defect in whom it is likely that the muscle which had regressed since birth has developed again.[29] Vasomotor tone now has been demonstrated in the pulmonary vessels of normal man,[10, 30] in patients with mitral stenosis associated with pulmonary hypertension,[9, 31] cor pulmonale,[20] and in idiopathic pulmonary hypertension.[20]

## Summary

Acetylcholine was administered by constant-rate infusion into the pulmonary arteries of 11 patients having pulmonary hypertension associated with atrial or ventricular septal defect.

The oxygen consumption, oxygen saturation in the pulmonary artery and systemic arterial blood, and the pulmonary artery pressure were recorded continuously before, during, and after the infusion. These data were used to determine changes in total pulmonary resistance during infusion of acetylcholine.

All 6 of the patients with atrial septal defects showed some decrease in resistance when receiving acetylcholine. If the pulmonary resistance when the patient was breathing air is taken as 100 per cent, the decrease was 23 (range 15 to 51) per cent with infusion of acetylcholine alone, 29 (range 9 to 33) per cent on breathing oxygen and 43 (range 27 to 60) per cent on breathing oxygen and receiving acetylcholine.

Of the 4 patients with only ventricular septal defect one did not respond to either oxygen or acetylcholine. For the remainder the average percentage decrease in resistance with acetylcholine while breathing air was 31 (range 10 to 69) per cent, while breathing oxygen 33 (range 25 to 66) per cent and while breathing oxygen and receiving acetylcholine 57 (range 35 to 74) per cent.

One patient with both an atrial and a ventricular septal defect showed no response.

As there was no evidence of a decrease in left atrial pressure with acetylcholine these changes in total pulmonary resistance demonstrated by the method employed presumably represent an actual reduction in pulmonary vascular resistance.

It is concluded that active constriction of pulmonary vessels can be an important factor in maintaining the high resistance to pulmonary blood flow found in some patients with congenital heart disease.

## Acknowledgment

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## Summario in Interlingua

Acetylcholina esseva administrate a 11 patientes con hypertension pulmonar in association con defectos atrio- o ventriculoseptal. Le administration del droga esseva effectuate per infusion in le arterias pulmonar sub conditiones de fluxo constante.

Ante, durante, e post le infusion, registrationes continue esseva obtenite de (1) le consumption de oxygeno, (2) le saturation oxygenic in le arterias pulmonar e le arterias del circulation systemic, e (3) le tension in le arterias pulmonar. Iste datos esseva utilisate pro determinar alterationes in le total resistentia pulmonar durante le infusion de acetylcholina.

Le 6 patientes con defectos atrio-septal monstrava omnes un certe mesura de reduc

ion del resistentia durante le infusion de cetylcholina. In comparation con le resistentia pulmonar durante le respiration de ere in le absentia de acetylcholina, le reduction amontava a un valor medie de 23 pro cento (minimo-maximo: 15 a 51) con le infusion de acetylcholina e le respiration de ere, de 29 pro cento (minimo-maximo: 9 a 3) con le respiration de oxygeno sin infusion de acetylcholina, e de 43 pro cento minimo-maximo: 27 a 60) con le infusion de acetylcholina e le respiration de oxygeno.

Inter le 4 patientes con solmente defectos ventriculo-septal, un respondeva a ni oxygeno ni acetylcholina. Inter le alteres, le procentage medie del reduction del resistentia con infusion de acetylcholina e respiration de aere esseva 31 (minimo-maximo: 10 a 69), con respiration de oxygeno e sin infusion de acetylcholina 33 (minimo-maximo: 25 a 66), e con respiration de oxygeno e infusion de acetylcholina 57 (minimo-maximo: 35 a 74).

Un patiente con defecto atrio-septal e defecto ventriculo-septal monstrava nulle responsa.

Viste que nihil indicava le occurrentia de un reduction del tension sinistro-atrial como effecto del acetylcholina, le alterationes del total resistentia pulmonar demonstrate per le methodo empleate representa probibilemente un genuin reduction del resistentia pulmono-vascular.

Es concludite que le constriction active del vasos pulmonar pote esser un factor importante in mantener le alte resistentia al fluxo pulmonar de sanguine que es notate in certe patientes con congenite morbo cardiac.

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# Effect of Acetylcholine on Pulmonary Vascular Resistance in a Patient with Idiopathic Pulmonary Hypertension

*By* ROBERT J. MARSHALL, M.D., M.R.C.P., H. FREDERIC HELMHOLZ, JR., M.D., AND JOHN T. SHEPHERD, M.D., MCH., D.SC.

Necropsy studies in cases of pulmonary hypertension of unknown cause show structural changes in the pulmonary vessels that are called irreversible. Acetylcholine chloride was infused at a rate of 2 mg. per minute into the outflow tract of the right ventricle of a 48-year-old woman who had pulmonary hypertension. The mean pulmonary artery pressure decreased from 56 to 25 mm. Hg and the pulmonary flow increased slightly. These findings are consistent with the theory that so-called idiopathic pulmonary hypertension may at some stage be maintained by vasoconstriction.

MUCH debate has centered around the question of pulmonary vasomotor activity in man. Daly[1] stated that none of the observations on human beings so far reported fulfills all of the criteria that are essential for the demonstration of an active control. It is difficult to measure accurately changes in resistance to flow offered by the pulmonary vessels and to decide whether these changes actually represent significant alterations in vessel caliber. Calculation of this resistance requires the simultaneous measurement of pulmonary artery and pulmonary artery wedge (left atrial) pressure and pulmonary blood flow under conditions in which the state of the subject remains steady.[2]

In patients with idiopathic pulmonary hypertension in whom the left atrial (pulmonary artery wedge) pressure is normal, a large pressure gradient is present across the pulmonary vascular bed. Thus, the absolute errors in measuring changes in perfusion pressure are relatively minor in comparison with the normal situation, in which only a small pressure gradient is present.

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The patient was a 48-year-old woman who had 4 children, aged 10 to 18 years. There was no evidence of pulmonary disease or a history to suggest pulmonary emboli. Her main complaint was effort dyspnea with a gradual onset about 3 years prior to the present examination; the dyspnea varied subjectively from day to day, had not manifested recent progression, and caused only slight disability.

The essential findings at cardiac catheterization are summarized in table 1. The arterial oxygen saturation and the pulmonary artery wedge pressure were normal, and the saturation data gave no evidence of any

TABLE 1.—*Oxygen Saturation and Pressures during Cardiac Catheterization in a Patient with Pulmonary Hypertension**

| Site | Blood oxygen saturation, per cent (cuvette oximeter) | Pressure (mm. Hg) |
|---|---|---|
| Inferior vena cava | 78 | 3 (mean) |
| Right atrium | 77 | 3 (mean)† |
| Superior vena cava | 76 | 3 (mean) |
| Right ventricle | 77 | 78/4 |
| Pulmonary artery | 77 | 78/36 |
| Pulmonary artery wedge | 99 | 8/2 (mean of 5) |
| Radial artery | 98 | 136/78 |

*Oxygen capacity=18.1 volumes per cent.

†The "a" wave was prominent and measured 7 mm. Hg.

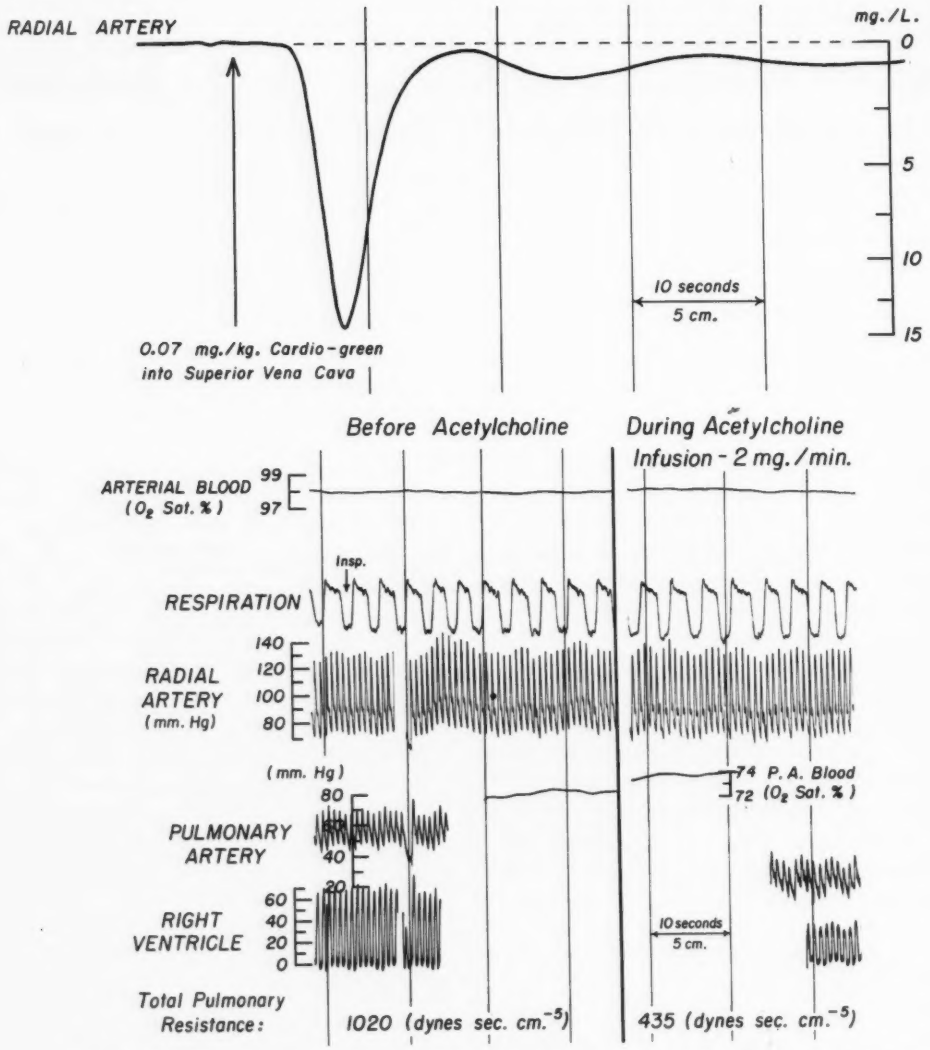


FIG. 1 *Top.* Dye-dilution curve from radial artery after injection of 5 mg. of cardiogreen (*arrow*) into superior vena cava.

FIG. 2 *Bottom.* Part of original photokymographic record before and during infusion of acetylcholine chloride at a rate of 2 mg. per minute into outflow tract of right ventricle.

shunt. A dye-dilution curve obtained by injecting 5 mg. of cardiogreen dye* into the superior vena cava and sampling blood from the right radial artery did not indicate a venoarterial shunt, and the normal contour of the disappearance slope and the first recirculation phases was consistent with the absence of an arteriovenous shunt[3] or valvular incompetence[4] (fig. 1).

*Hynson, Westcott and Dunning, Baltimore, Md.

## METHODS

Catheters were placed into the pulmonary artery just above the valve and into the right ventricle. The pressure in the radial artery was measured by a strain-gage manometer, and the arterial oxygen saturation was determined by an ear oximeter. Tidal volume and oxygen consump

TABLE 2.—*Effect of Infusion of Acetylcholine Chloride (2 mg./min.) into Outflow Tract of Right Ventricle*

| | Breathing air | | Breathing air | | Breathing oxygen | |
|---|---|---|---|---|---|---|
| | Before infusion | During infusion | Before infusion | During infusion | Before infusion | During infusion |
| $O_2$ content rt. vent. blood (vol. %) | 12.8 | 13.1 | 12.8 | 13.2 | 14.4 | 15.0 |
| $O_2$ content radial art. blood (vol. %) | 17.7 | 17.7 | 17.7 | 17.7 | 19.2 | 19.2 |
| Pulm. blood flow (L./min.) | 4.4 | 4.6 | 4.4 | 4.8 | 4.5 | 5.1 |
| Mean pulm. artery pressure (mm. Hg) | 56 | 25 | 56 | 27 | 60 | 32 |
| Total pulmonary resistance, dynes sec. cm.$^{-5}$ | 1020 | 435 | 1020 | 450 | 1065 | 500 |

tion before, during, and after the infusion were monitored by a closed-circuit spirometer. Acetylcholine chloride was infused into the right ventricle at a constant rate over a period of 1½ to 2 minutes by a syringe driven by compressed air. The catheter in the pulmonary artery was used alternately to monitor pressure by means of a strain-gage manometer and to monitor oxygen saturation by means of a cuvette oximeter before, during, and after the infusion. As a safety measure, a dose-response curve was carried out. The data reported are those obtained with a dose that had a maximal effect on the pulmonary vessels with minimal systemic or respiratory side effects, namely 2 mg. of acetylcholine chloride per minute, dissolved in 12 ml. of an isotonic solution of sodium chloride. For the calculation of pulmonary blood flow, the oxygen content of pulmonary artery and radial artery blood was obtained from the blood oxygen capacity estimated by the method of Sendroy[5] as modified by Roughton and associates[6] and from the percentage of oxygen saturation in the pulmonary artery and in arterial blood measured by the cuvette and the earpiece oximeter, respectively. Pulmonary resistance expressed in dynes seconds centimeter$^{-5}$ was calculated from the following ratio:

$$\frac{\textit{Pulmonary-artery mean pressure (mm. Hg)} \times 1332}{\textit{Pulmonary blood flow (ml./sec.)}}$$

## RESULTS

Figure 2 shows selections from the photokymographic record before and during administration of acetylcholine at the rate of mg. per minute with the patient breathing air. During the infusion, no change occurred in the oxygen saturation of systemic arterial blood as indicated by the ear oximeter, in radial artery pressure or in pulse rate. The respiratory rate decreased slightly. The oxygen saturation of the pulmonary artery blood increased, and a pronounced decrease in pulmonary artery and right ventricular pressure occurred.

The simultaneous spirometric tracing gave no evidence of a change in oxygen consumption. Therefore, these findings suggest a slight increase in pulmonary blood flow associated with the great decrease in pulmonary artery pressure.

The infusion of acetylcholine was repeated with the patient breathing air and subsequently breathing 99.8 per cent oxygen. The results were similar on all 3 occasions (table 2).

## DISCUSSION

The pulmonary artery wedge pressure was not measured during the administration of acetylcholine; since the systemic arterial pressure and the pulse rate remained constant, it is unlikely to have changed. Had it increased, the perfusion pressure would have been even less than that calculated. Had it decreased to zero from the preinfusion level of 5 mm. Hg, this would not have affected our conclusions. Hence, the demonstrated decrease in total pulmonary resistance indicates a similar decrease in pulmonary vascular (arteriolar) resistance.

It is difficult to say what degree of decrease in resistance provides certain evidence of vasodilatation. Other workers have

shown that resistance in some patients with idiopathic pulmonary hypertension decreases after single injections of "Priscol"[7, 8] and acetylcholine.[9] In the present studies, in which a steady cardiorespiratory state was maintained by continuous infusion of acetylcholine, the mean pulmonary artery pressure decreased from 56 to 25 mm. Hg, while the flow increased slightly. The oxygen saturation of systemic arterial blood, the systemic arterial pressures, and the heart rate were unchanged. Therefore, it is difficult to believe that these findings can be explained other than through a decrease in activity of smooth muscle in vessels somewhere in the lungs.

The breathing of oxygen instead of air can result in a decrease in pulmonary vascular resistance in some patients who have pulmonary hypertension associated with congenital heart disease.[10, 11] In the present case, the breathing of oxygen alone had no effect, nor did it enhance the response to acetylcholine.[12]

The present observations support the conclusion of other workers[7–9] that active constriction of pulmonary vessels may play an important role in maintaining the pulmonary hypertension in such patients. The nature of this constriction has yet to be elucidated, but it has now been demonstrated in some patients with every disease of the heart or great vessels with which pulmonary hypertension is associated.[9, 12–14]

## Summary

Acetylcholine chloride was infused at a rate of 2 mg. per minute into the outflow tract of the right ventricle of a 48-year-old woman who had idiopathic pulmonary hypertension. A steady cardiorespiratory state was achieved by this continuous infusion. The mean pulmonary artery pressure decreased from 56 to 25 mm. Hg and the pulmonary blood flow increased slightly. The pulmonary vascular resistance was thus reduced from 1020 to 435 dynes seconds centimeter$^{-5}$. The oxygen saturation of systemic arterial blood, the systemic arterial pressure, and the heart rate were unchanged. These results demonstrate that constriction of pulmonary vessels played an important role in maintaining the pulmonary hypertension in this patient. The mechanism by which the constriction originates and is maintained is unknown.

## Summario in Interlingua

Chloruro de acetylcholina esseva infundite, a 2 mg per minuta, in le tracto de efflux del ventriculo dextere de un femina de 48 annos de etate qui habeva idiopathic hypertension pulmonar. Stabilitate del stato cardiorespiratori esseva effectuate per un infusion continue. Le valor medie del tension pulmono-arterial descendeva ab 56 a 25 mm de Hg, e le fluxo pulmonar de sanguine se augmentava levemente. Le resistentia pulmono-vascular esseva reducite assi ab 1020 a 435 dyna-secunda-centimetro$^{-5}$. Le saturation oxygenic de sanguine arterial in le circulation major, le tension del sanguine arterial in le circulation major, e le frequentia cardiac remaneva inalterate. Iste resultatos demonstra que le constriction es producite e per le qual illo es mantenite remane incognoscite.

## Acknowledgment

The authors wish to thank Dr. E. H. Wood for his participation in this study and Drs. R. O. Brandenburg, H. W. Marshall, and R. D. Miller for their cooperation. Roche Products, Ltd., Welwyn Garden City, England, and Hoffman-LaRoche, Inc., Nutley, N. J., kindly supplied us with the ampules of acetylcholine chloride.

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Likewise, all studious, good and honest men, do never suffer their mind so to be o'rwhelm'd with the passions of indignation and envy, but that they will patiently hear what shall be spoken in behalf of the truth, or understand any thing which is truly demonstrated to them; nor do they think it base to change their opinion, if truth and open demonstration so perswade them, and not think it shamefull to desert their errors, though they be never so antient, seeing, they very well know that all men may erre, and many things are found out by chance, which any one may learn of another, an old man of a child, or an understanding man of a fool.—WILLIAM HARVEY. *De Motu Cordis,* 1628.

# A Syndrome Featuring Defects of the Heart, Sternum, Diaphragm, and Anterior Abdominal Wall

*By* I. Hunter Crittenden, M.D., Forrest H. Adams, M.D., and Donald G. Mulder, M.D.

Three patients featuring a syndrome of defects of the heart, sternum, diaphragm, and anterior abdominal wall are presented. The striking similarity of the anomalies manifested by the 3 cases posed a question whether or not a recognized syndrome previously existed. In order to determine this, a search was made to find other such cases, and an attempt was made to establish a common embryologic pathogenesis. Review of the literature as well as extensive personal communication was carried out. Embryology of the involved organs was considered in order to determine a specific phase of defective development.

THREE patients with congenital defects involving the heart, diaphragm, lower sternum, and anterior abdominal wall have been recently studied at the University of California at Los Angeles. The features that characterize these patients are (1) malrotation of the heart with dextroposition, (2) intracardiac anomalies including ventricular septal defect, (3) deficient lower sternum, (4) anterior diaphragmatic defect, and (5) midline abdominal defect with diastasis recti and umbilical hernia. These unusual but strikingly similar features suggested a specific syndrome.

## Case Reports

*Case 1.* M.M. was admitted, at age 11 months to the U.C.L.A. Hospital. The pregnancy was complicated by ingestion of quinine and by minimal vaginal bleeding at 6 weeks' gestation. At 1 day of age, a 3 by 3 cm. omphalocele was repaired at another hospital without incident. Repeated respiratory infections marked the infancy period, requiring hospitalization 6 times. At 4 months of age, cyanosis was first noted during crying by the mother. A heart murmur was first detected by the family physician at 5 months of age. Weight gain was slow, but motor and social development were normal. The family history was unremarkable.

Physical examination showed an underdeveloped alert Caucasian infant with mild tachypnea but in no acute distress. The blood pressure was 70 mm. Hg in the upper and lower extremities by the simultaneous flush technic. The pulse was 12[illegible] per minute, and the respirations were 30 per minute. The height was 69 cm. and the weight 6.[illegible] Kg., which placed the patient in the seventy-eighth percentile on the Wetzel grid. The mandible was somewhat underdeveloped. Circumoral cyanosis occurred with crying. There was no clubbing of the digits. Bilateral costal flaring and midline chest prominence were present. The lower sternum was deficient, with a vestigial unilateral xiphoid process palpable to the left of the midline cleft extending to the fifth rib. Cardiac pulsations and a protuberance were visible extending 3 cm. below the apex of the sternal cleft as shown in figure 1. A 4-cm. diastasis recti, covered by skin, extended to the repaired omphalocele. Examination of the heart revealed a sinus rhythm with a markedly accentuated and slightly split pulmonic second sound. Cardiac dullness was greater to the right of the sternum. A grade III rough systolic murmur not associated with a thrill was present low at the right sternal border. Femoral pulsations were full. The hemoglobin was 12.2 Gm. per cent and the hematocrit level was 40 per cent.

The electrocardiogram was abnormal, showing right-axis deviation, upright P waves, and inverted T waves in leads I and II and a prominent Q wave in lead I. There was no conduction delay. The T waves were upright in the conventional unipolar precordial leads, and the voltage of all waves was normal.

As shown in figure 2, roentgenograms demonstrated an unusual cardiac configuration with dextroposition, plethoric lung fields, and a deficiency of the lower sternum and of the anterior diaphragm. (The lead marker identifies the apex of the sternal cleft.)

Cardiac catheterization was performed under rectal basal anesthesia. The unusual position of the catheter in the right and in the left ventricles

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shown in figure 3. The right ventricular systolic pressure equaled the left ventricular systolic pressure of 100 mm. Hg. A large left-to-right as well as a small right-to-left interventricular shunt was demonstrated.

Selective angiocardiography from the right ventricle showed the right ventricle to be at the far right anterior heart border and somewhat superior to its usual position as shown in figure 2. The pulmonary outflow tract crossed from the right to the left side of the heart superiorly and anteriorly. The aorta descended on the left. Definitive surgery was deferred due to the likelihood of a markedly deficient ventricular septum which was deemed not repairable by existing technics. When seen last at 16 months of age, the patient was doing well and had been free of infection for 4 months.

*Case 2.* D.H. was admitted to the U.C.L.A. Hospital at 22 months of age for right heart catheterization. He was adopted at 8 days of age, and a heart murmur was noted at that time. Nothing was known of the family history or gestational period. Growth and development were normal. The only recognized cardiac symptom was mild exertional dyspnea. Physical examination revealed a well nourished, active 22-month-old Caucasian boy in no distress. The blood pressure was 80 mm. Hg in the upper and 90 mm. Hg in the lower extremities by the simultaneous flush technic. The pulse was 92 per minute and the respirations were 24 per minute. Slight nailbed cyanosis associated with mild clubbing was present. The anterior chest bulged in the midline and there was bilateral costal flaring. The lower sternum was deficient and there was a rudimentary unilateral xiphoid process palpable along the right costal margin near the apex of the sternal cleft. Extending 3 cm. below the deficient sternum could be seen a pulsating mass beneath the skin covering a 4-cm. rectus separation as shown in figure 4. A 2-cm. umbilical hernia was present. The cardiac dullness was greater to the right than to the left of the sternum. A grade IV harsh systolic murmur associated with a thrill was heard best low along the right sternal border. The pulmonic second sound was quiet.

The electrocardiogram showed inversion of T waves and upright P waves in leads I and II. A prominent Q wave was present in lead I. The R wave in lead II was 3 mm. Axis deviation was right. No conduction delay was present. R waves were upright from $V_1$ through $V_6$. The hemoglobin was 15.2 Gm. per cent and the red blood cell count 5.2 million per mm.$^3$ Roentgenograms demonstrated dextroposition and an unusual configuration of the heart as shown in figure 5. The pulmonary vascularity was unremarkable.

Cardiac catheterization was performed under

FIG. 1. Case 1, M.M., age 11 months. The pulsating cardiac mass can be seen in the epigastrium below the cleft lower sternum. Costal flaring and a repaired omphalocele are demonstrated.

rectal basal anesthesia. The unusual position of the right and left ventricles with the catheter in them is similar to that shown in figure 3. The systolic pressure in each ventricle was 105 mm. Hg. The right atrial pressure was elevated to 23/7 mm. Hg. A bidirectional interventricular shunt was present. Cardiac irritability prohibited attempts to enter the pulmonary artery. Selective angiography was performed from the right ventricle as shown in figure 5. The right ventricle was at the anterior right heart border with the pulmonary artery crossing anteriorly and superiorly to the left border of the heart. An infundibular pulmonary stenosis was demonstrated as was a right-to-left interventricular shunt with subsequent filling of a left-sided aorta. Definitive surgical repair was deferred pending progression of polycythemia or symptomatology.

*Case 3.* W.E. was first admitted to the U.C.L.A. Hospital at 5 months of age for treatment of a severe respiratory infection. He was born following a normal full-term pregnancy. At 1 month of age a heart murmur was heard by the family physician, and at 4 months of age a pulsating mass was noted in the epigastrium. Tachypnea and slow weight gain were apparent but motor development was normal.

He was readmitted at 11 months of age for heart catheterization. Physical examination on admission showed a healthy appearing noncyanotic Negro infant. The blood pressure was 90 mm. Hg in the upper and 80 mm. Hg in the lower extremities by the simultaneous flush technic. The chest bulged at the anterior midline and mild costal flaring was present bilaterally. The xiphoid process was absent. A 2.5-cm. diastasis recti extended to the umbilical hernia, which was 1 cm. in diameter. A mass beneath the skin could be seen and

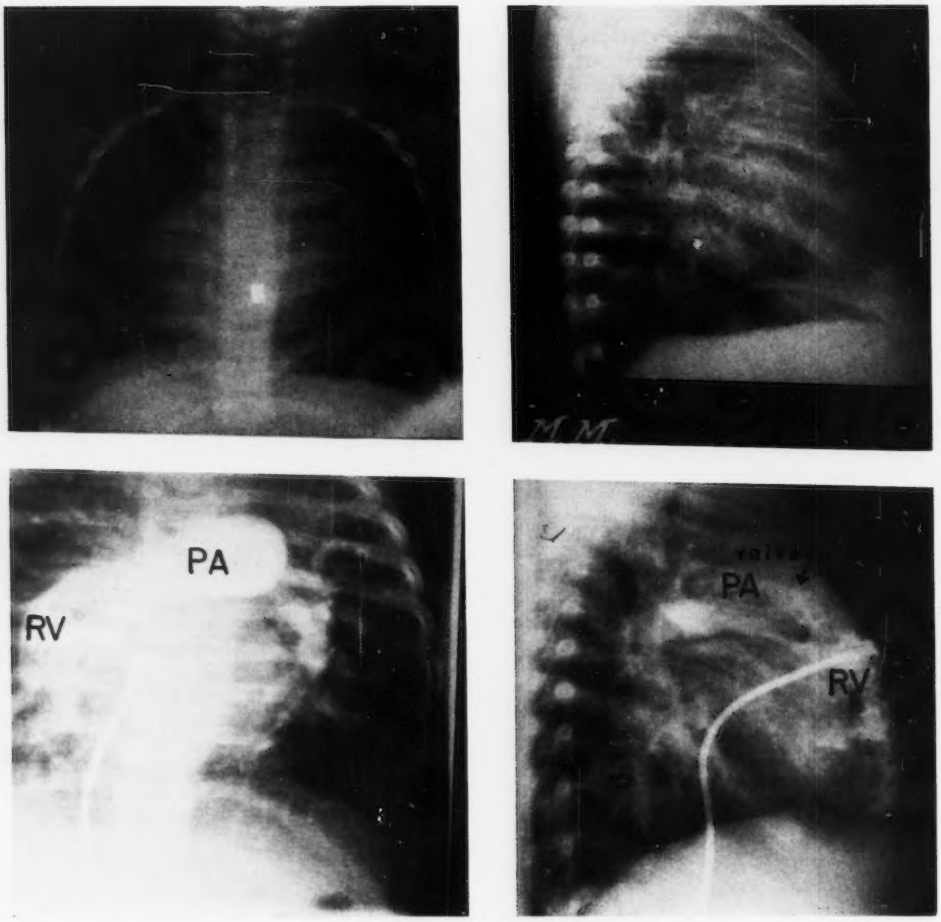


FIG. 2. Case 1, M.M. *Top.* Dextroposition of the heart and plethoric fields. *Marker,* apex of the sternal cleft. *Bottom.* Selective angiocardiogram from the right ventricle shows the right ventricle to be rotated to the far right anterior heart border with the pulmonary artery crossing to the left superiorly and anteriorly.

palpated to extend as a fingerlike projection one half the distance to the umbilicus. A distinct but synchronous pulsating mass was palpable just beneath the defective sternum as shown in figure 6. Cardiac dullness was predominantly on the right side. The pulmonic second sound was accentuated. A grade IV harsh systolic murmur associated with a thrill was heard best at the right lower sternal border. A loud to-and-fro systolic and diastolic murmur was prominent over the epigastric mass.

The electrocardiogram was abnormal showing upright P and inverted T waves in leads I and II. A prominent Q wave was present in lead I. There was no conduction delay. Axis deviation was right. T waves were upright in $V_1$ through $V_6$. The precordial QRS voltage was unremarkable.

The roentgenograms showed dextroposition of the heart with mild cardiomegaly and plethoric lung fields (fig. 7). There was evidence of an anterior diaphragmatic hernia. Cardiac catheterization was performed under rectal basal anesthesia. The bizarre position taken by the catheter in the right ventricle was similar to that shown in figure 3. The pulmonary artery and right ventricular pressure was elevated to 72 mm. Hg systolic. A large left to right interventricular shunt was found.

Selective angiography from the right ventricle

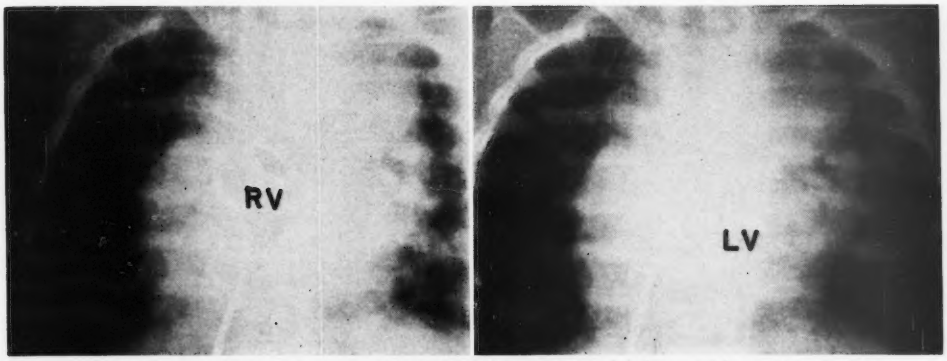


FIG. 3. Case 1, showing the unusual position of the right and left ventricles with a catheter in each.

demonstrated cardiac rotation with the right ventricle further to the right than usual and at the anterior right heart border. The pulmonary artery crossed anteriorly and superiorly to the left side (fig. 7). The suspected ventricular diverticulum was not outlined by the angiogram.

At 13 months of age, surgery was performed upon the patient. A sagittal exposure was made through a median sternotomy. A 3-cm. semilunar midline anterior diaphragmatic defect gave passage for a 3.5-cm. long diverticulum of the left ventricle covered by a membrane, presumably pericardium (fig. 8). The actual position of the heart was as suggested from the angiocardiogram. A prominent sagittal sulcus separated the right and left ventricles in the sagittal plane with the right ventricle somewhat superior to the left. The atria were in their usual positions. A right ventricular cardiotomy exposed an interventricular septal defect, 1 cm. in diameter, in the membranous portion a few millimeters below the aortic valve. Primary closure of the defect was made using interrupted silk sutures. Following this the diverticulum from the left ventricle was amputated at the base. This unusual tubular structure originated from the left ventricle as a thin-walled muscular stalk with an internal diameter of about 2 mm. The stalk ballooned out in the form of a sac at the distal portion and was covered by a membrane. A few ligamentous strands connected this structure to the liver capsule. Repair of the anterior diaphragmatic defect was incorporated in the closure of the thoracotomy as was approximation of the rectus muscles at the midline. Postoperative recovery was uneventful. When last seen, at 15 months of age, the patient was doing well.

## DISCUSSION

Remarkably consistent features of the cases seen by us are the ventral abdominal wall de-

FIG. 4. Case 2, D.H., age 22 months. The epigastric pulsating cardiac mass is shown below the cleft lower sternum. Bilateral costal flaring and an umbilical hernia are apparent.

fects and the unusual positional relationship of the heart within the thorax. This position of the heart can best be described as a 90° rotation on the longitudinal axis, so that the right ventricle comes to lie farther to the right than it normally does, and a rotation on the dorsoventral axis, so that the right ventricle comes to lie somewhat superior to its usual position.

Another feature common to these cases is that the electrocardiograms show upright P waves and inverted T waves in leads I and II; a prominent Q wave in lead I and upright T waves in $V_1$ through $V_6$. This is not typical of dextrocardia but suggests rotation of the ventricles with the atria in the usual position. Each of the patients had an interventricular septal defect; in one it was associated with

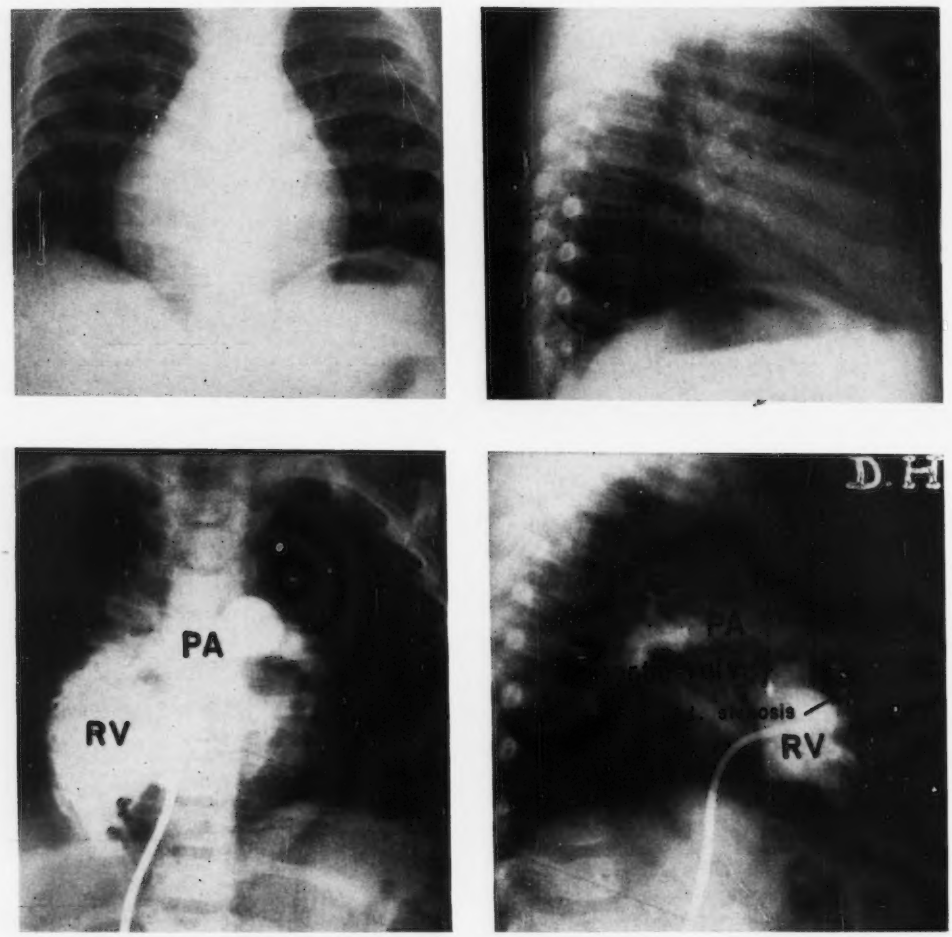


FIG. 5. Case 2, D.H. *Top.* Dextroposition of the heart. A deficiency of the lower sternum is indicated by the lead marker. *Bottom.* Selective angiocardiography from the right ventricle shows the right ventricle to be rotated to the far right anterior heart border. Dye demonstrates an infundibular pulmonary stenosis and a right-to-left interventricular shunt with filling of the left-sided aorta.

infundibular pulmonary stenosis and in another with a diverticulum of the left ventricle. The sternal defect varied from a rudimentary xiphoid process to a cleft lower sternum. The anterior median diaphragmatic defect and deficient lower sternum permitted cardiac impulses to be seen and felt in the epigastrium beneath the skin covering the diastasis recti.

The combination of anomalies presented by us has been in essence previously reported and probably erroneously categorized as a subgroup of ectopia cordis.[1, 2] Ectopia cordis was first described by Haller in 1706.[3] Todd[4] in 1836 classified the disease into 3 types: cervical, thoracic, and abdominal. In the thoracic type, a cleft sternum is present; a cleft sternum is not always associated with ectopia cordis. Grieg[5] in 1926 reported 20 cases with varying degrees of sternal clefts which did not have ectopia cordis. Only one of his cases had intracardiac anomalies. Grieg[5]

and others[6, 7] have presented cases of ectopia cordis of the cervical, thoracic, and abdominal variety. A diaphragmatic hernia with a normal sternum and an abdominal heart characterized the abdominal type.

Byron[1] in 1942 summarized 142 cases from the literature and added a fourth category called thoracoabdominal ectopia cordis, which manifested a defective sternum plus abdominal involvement.

Major[2] in 1953 reviewed all the cases that could be classified thoracoabdominal ectopia cordis according to Byron's terminology. The characteristics of this group were (1) partial absence or cleft of the sternum, (2) diaphragmatic defect, (3) midline abdominal defect with diastasis recti and omphalocele. A total of 15 cases was presented. Twelve died before 4 months of age. Two have had their epigastric defects successfully repaired and are living. Little mention was given specific cardiac position and function. These 15 cases probably represent the same syndrome as do our patients.

Cantrell, Haller, and Ravitch[8] recently collected 5 cases similar to ours. All 5 had ventricular septal defects; in 2 there was associated pulmonary stenosis, and in 2 there was associated a diverticulum of the left ventricle.

It is our contention that this syndrome should not be classified as ectopia cordis. Maude Abbott[9] defined ectopia cordis as "a displacement so that the heart passes out of the thorax and comes to be either upon the outer surface of the body or in the abdominal cavity." The principal characteristic feature of our cases is the dextroposition and rotation of the heart within the thoracic cage.

The syndrome of dextroversion of the heart not associated with ventral abdominal wall defects was recently reviewed by Grant.[10] This syndrome included many cases previously reported as isolated dextrocardia. Typically the heart was rotated so that the right ventricle came to lie farther to the right than usual "as in turning the pages of a book 90°," and appeared in dextroposition. The positions of the right ventricle and pulmonary artery as shown by angiography were identical to the cases described here. Intracardiac anomalies including interventricular septal defect were usually present. We have studied 3 such patients in whom the heart lay in this position, 1 with tetralogy, and 2 with interventricular septal defects, without any evidence of abdominal wall anomalies.

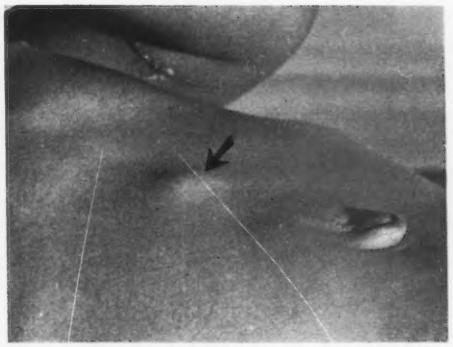

FIG. 6. Case 3, W.E., age 11 months. The diverticulum from the left ventricle is noted as a mid-epigastric pulsating mass. Costal flaring and an umbilical hernia are apparent.

## EMBRYOLOGY

In considering the embryology, as with most of the congenital defects, the end result is known and something of the steps by which they were arrived at, but virtually nothing is known about the actual causative factors. The problem can be approached by considering briefly the development of the organs involved.[11-13]

The cardiopericardial primordium begins as a paired zone of thickened mesoderm near the cephalic end of the embryo and with the formation of the head fold, and the lateral body folds, the pericardial cavity is swung beneath the pharynx. The splanchnic mesoderm forming the ventral part of the anterior intestinal portal also forms the caudal wall of the pericardial cavity. According to Patten[11] this shelf of tissue is the transverse septum.

Thus the pericardial cavity is surrounded from at least the third week of development, by a thin but complete thoracic wall, consisting of a simple layer of ectoderm and a layer of somatic mesoderm. Into this thin wall the

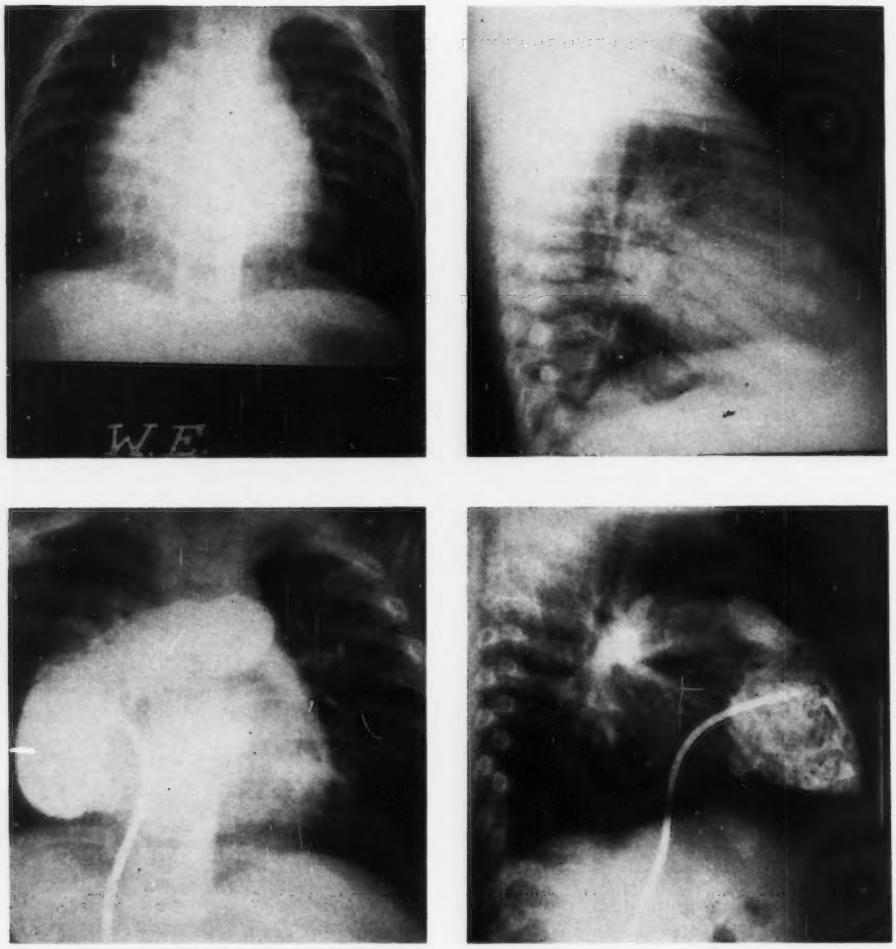


FIG. 7. Case 3, W.E. *Top.* Mild cardiomegaly, plethoric lung fields, and dextroposition of the heart. *Bottom.* Selective angiocardiography from the right ventricle shows the right ventricle to be rotated to the far right anterior heart border with the pulmonary artery crossing to the left anteriorly and superiorly.

sclerotome, the myotome, and the dermatome migrate, thickening it. This thickening progresses until the masses meet and fuse in the ventral midline. This fusion begins cephalically and progresses caudally toward the umbilicus, being essentially complete by the eighth week. Subsequently the cartilage anlagen of the sternum differentiate and fuse in the same cephalocaudal direction. The ventral edge of the myotomes of the lumbar segments differentiate into the rectus columns, forming the rectus abdominis muscles.

The endodermal cells of the developing liver grow out into the transverse septum, leaving a layer of mesoderm on its cephalic surface which subsequently differentiates into the "central tendon" of the diaphragm. Somite muscle from cervical segments 3-4-5 comes to lie within the lateral part of the diaphragm, most of which part has arisen from the pleuroperitoneal folds.

There is some reason to believe that some of the lateral part of the diaphragm is derived from the lateral body wall. If this proc-

s of contribution to the diaphragm from ıe body wall also involves the ventral part which seems likely, although there is no roof of this in the literature),[13] then the ntral midline part of the diaphragm could expected to be abnormally weak, as was ıe adjacent part of the body wall itself. This akes plausible a caudad outpouching of the eakened membranous part of the diaphragm ı the midline at a point where it is least inforced by the liver, i.e., ventrally. Into is pouch a diverticulum of the ventricle ould project.

The organs just considered all have an inimate final relationship to each other. To the ower sternum or xiphoid process attach the nterior leaf (septum transversum) of the diaphragm, the linea alba, and medial fibers of the rectus abdominus muscle. By about 8 weeks these structures normally are united and fused in the midline. The causative factor for failure of normal fusion is speculative.

Since the skin was intact and presumably normal in the ventral midline, it is probable that there was no early defect in the lateral body folds and in the isolation of the pericardial cavity, such as occurs in cases when the heart is exposed on the surface of the chest.[13]

It seems that the basic defect in these 3 cases was a failure of the mesoderm of the body wall to complete its migration to meet and fuse solidly in the ventral midline. This would account for the failure to fuse of the sclerotome (cleft sternum and xiphoid process) and of the myotome (diastasis recti). This general failure also explains the presence of the omphaloceles, or umbilical hernias.

The positional relationship of the heart is an interesting consideration. It suggests embryonic arrest with failure of complete rotation and bending to the left. The interventricular septum membranaceum is formed by the union of 3 parts: the descending conus ridge, the endocardial cushions, and the ascending ventricular septum. The conus and truncus ridge divides the outlet of the heart equally into the pulmonary artery and aorta by means of spiral torsion. The union of these

FIG. 8. Case 3, W.E.; heart exposed at the time of surgery. The diverticulum from the left ventricle is shown overlying a crescent-shaped midline diaphragmatic defect. A sagittal sulcus can be seen separating the 2 ventricles thus demonstrating the abnormal rotation of the heart to the right.

3 structures to form the intact ventricular septum occurs at about the eighth week and is dependent upon precise positional timing. Failure of complete rotation of the heart to the left, which normally occurs by the seventh week, could influence such a union.

A common gestational time can be presumed for the occurrence of the defects described but no causative factor can be explained other than failure of the body wall mesoderm of complete migration and fusion in ventral midline.

One can expect to find variation in cases of this type. Whether the same basic pathogenesis, differing only in degree, is responsible for mere dextroversion of the heart in one case and complete ectopia cordis in another is conjecture. Suffice it to say that the cases herein reported are sufficiently distinct to be considered a syndrome.

## Summary

Three patients are reported who manifested unusual but strikingly similar features. These include (1) cardiac malrotation with dextroposition, (2) intracardiac defects including ventricular septal defect, (3) deficient lower sternum, (4) anterior diaphragmatic defect, and (5) midline abdominal defect with diastasis recti and umbilical hernia. The midline deficiency permitted cardiac impulses to be seen and palpated in the epigastrium.

The rotational position of the heart was demonstrated in each by selective angiography and electrocardiography. One case was operated upon and complete surgical repair of the defects, including amputation of a diverticulum from the left ventricle, was successful.

Review of the literature showed cases resembling ours to have been previously classed as a rare subgroup of ectopia cordis. This is probably erroneous classification, and these patients should be considered as comprising a distinct syndrome. Consideration is given to possible embryologic pathogenesis.



## Acknowledgment

The authors are indebted to Bernard J. O'Loughlin, M.D., Head of the Division of Diagnostic Radiology, for his help in the radiologic interpretations of these patients.



## Summario in Interlingua

Es reportate le casos de tres patientes con inusual sed frappantemente simile characteristicas pathologic. Istos include (1) malrotation cardiac con dexteroposition, (2) defectos intracardiac incluse un defecto ventriculo-septal, (3) deficientia del sterno inferior, (4) defecto antero-diaphragmatic, e (5) defecto centro-abdominal con diastasis de recto e hernia umbilical. Le defecto centro-abdominal permitteva vider le impulsos cardiac e palpar los in le epigastrio.

Le position rotational del corde esseva demonstrate in le tres casos per selective angiographia e electrocardiographia. In un del casos, un intervention chirurgic esseva effectuate pro reparar omne le defectos. Le operation succedeva, incluse le ablation de un diverticulo in le ventriculo sinistre.

Un revista del litteratura resultava in le constatation que casos simile a illos del presente reporto esseva classate in le passato como un rar sub-gruppo de ectopia del corde. Isto es probabilemente erronee. Iste patientes deberea plus tosto esser considerate como representante un syndrome distincte. Es considerate le possibilitate de un pathogenese embryologic.


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# Dicumarol, Coumadin, Marcumar and Tromexan

## Comparative Study of Their Action on the Clot as Registered by the Thrombelastogram

*By* JORGE ESCUDERO, M.D., ELLEN MCDEVITT, M.D., AND IRVING S. WRIGHT, M.D.

There is considerable interest and some difference of opinion about the relative clinical usefulness of many oral anticoagulant agents. In this study the more commonly used agents are evaluated with respect to their action on the clotting process as measured by thrombelastography. This test does not necessarily provide an evaluation of all aspects of the clinical action of an anticoagulant.

THE actions of the various coumarin derivatives are not fully understood. Dicumarol (3-3′-methylenebis-4-hydroxycoumarin) has been shown to be an effective anticoagulant and is most widely used. However, a search for the ideal anticoagulant[1] continues. Coumadin [3-(alpha-acetonyl benzyl)-4-hydroxycoumarin], Marcumar [3-(1′-phenylpropyl)-4-hydroxycoumarin] and Tromexan [3,3′-carboxymethylenebis (4-hydroxycoumarin) ethyl ester], have been claimed to possess different properties in some regards; for instance, varying deviations of action and elimination, cost, and incidence of hemorrhage.[1-12] However, the mechanism through which these 4 anticoagulants prolong the prothrombin time is essentially alike. Therefore, one would also expect them to act similarly on the physical properties of the clot. This study was designed to examine this theoretical supposition, the thrombelastograph being used to register the formation and firmness of the clot.[13]

### MATERIAL AND METHODS

Eight patients from the Anticoagulant Clinic of the New York Hospital were selected for this study. There were 3 women and 5 men, ranging in age from 33 to 76, with a mean age of 57 years. They had been on long-term anticoagulant therapy for different conditions. The 3 with rheumatic heart disease, mitral stenosis, and atrial fibrillation had suffered several thromboembolic episodes; one of them had 2 pulmonary infarctions, another had multiple emboli to the legs, and the third had emboli to various segments of the vascular tree. One patient had mild essential hypertension, generalized arteriosclerosis, and thrombosis of both popliteal arteries. Two patients had generalized arteriosclerosis, one with intermittent insufficiency of the internal carotid artery and the other with thrombosis of the same artery. The last 2 patients, both young men, had shown a marked thrombophilic tendency: one of them had migratory thrombophlebitis and the other had suffered 2 cerebral thromboses, thrombophlebitis of the right great saphenous vein, 2 pulmonary infarcts, and 1 myocardial infaret. Each of these patients was started on 1 of the 4 anticoagulants mentioned above in the doses generally accepted in clinical practice:[3, 6, 8-10, 12]

| | | |
|---|---|---|
| Dicumarol: | Initial, | 200 to 300 mg. |
| | Subsequent, | 25 to 100 mg. |
| Coumadin: | Initial, | 50 to 75 mg. |
| | Subsequent, | 5 to 10 mg. |
| Marcumar: | Initial, | 18 to 21 mg. |
| | Subsequent, | 3 to 9 mg. |
| Tromexan: | Initial, | 1200 to 1500 mg. |
| | Subsequent, | 150 to 600 mg. |

No uniform sequence was followed for the administration of anticoagulants. The patients received one type until the prothrombin time reached the therapeutic levels (25 to 35 seconds undilute, 70 to 160 seconds dilute). At this point, blood was taken and thrombelastograms were performed. The first anticoagulant was then stopped for 3 to 4 days and a second was administered until the prothrombin time was again within therapeutic levels. A new thrombelastogram was then obtained. Except for Tromexan,

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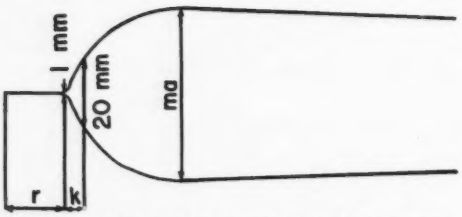


FIG. 1. Scheme of a normal thrombelastogram.

the elimination of the coumarin derivatives used is slow, sometimes continuing for 8 days or even longer.[2, 8] Subsequent determinations of the prothrombin times and thrombelastograms were therefore performed at least 1 week after the preceding anticoagulant was discontinued, when its effect was insignificant or entirely eliminated. This regimen was repeated until each patient had been tested with each agent. In addition to the 4 thrombelastograms taken from each patient while on anticoagulants, one was recorded while each patient was entirely free from the effects of anticoagulants and when the prothrombin time was normal (this value is referred to as the control).

The mechanism and principles of the thrombelastograph have been described by several authors.[14-26]

In brief, with this machine it is possible to see and to register the elastic variations of the thrombus during the coagulation process. The determinations can be carried out with either whole blood or citrated plasma. The specimen is placed in a steel cylinder mounted on a metal bar. This cylinder is slowly rotated to and fro mechanically over an angle of 4°45′. A piston dips into the blood. As long as the blood remains liquid before the process of coagulation is initiated to a significant degree, the movement of the cylinder is not transmitted to the piston, but when coagulation starts this begins to turn with the cylinder. The movement increases proportionally with the progressive development of fibrin and the solidification of the clot, until a maximal displacement is reached. Then, the amplitude of the movement decreases slowly with the flaccidity of the thrombus until complete fibrinolysis is obtained. The piston is suspended by a steel wire with high torsion elasticity. Attached to this wire is a mirror that reflects a light ray to a kymograph on which the tracing is recorded. The light is also reflected onto a glass scale, which permits the direct observation of the light movements. The temperature of the cylinder is maintained constant at 37 C. by a thermostat. Three specimens may be examined simultaneously in the 3 cylinders of the apparatus. The main components of the thrombelastogram are as follows (fig. 1): 1. The *reaction time* (*r*) characterized by a straight line. This value indicates the time interval between the recalcification of the plasma or the drawing of the blood, and the first signs of resistance due to fibrin formation. 2. The *coagulation time* (*k*) measured from the end of *r* to a point where the 2 lines of the graph are 2 cm. apart. This value represents the clot formation time. 3. The *maximal amplitude* (*ma*) of the graph, measured where the 2 lines are farthest apart. This value is related to the maximal elasticity of the clot (*mE*).

*Procedure.* For this study we used whole blood instead of citrated and recalcified plasma because we have found it more satisfactory. The apparatus was heated for 30 minutes before the test. By venepuncture 6 ml. of fasting blood were obtained with a siliconized syringe. A stopwatch was started when the first drops of blood entered the syringe, in order to measure the "filling time Z" (from the drawing of the blood until the recording of the thrombelastogram was begun. This time was always 4 minutes (8 mm.), and it was added to the reaction time *r* obtained in the thrombelastogram. For the tests, 1.5 ml. of blood were used. Three tracings were run simultaneously, 0.36 ml. of blood being placed in each cylinder. The pistons were immersed in the blood and this was covered with mineral oil. At the end of 4 minutes, the lights on the glass scale were turned on and the tracings were registered during the subsequent 1½ hours. The reaction time *r*, coagulation time *k*, and maximal amplitude *ma*, were measured in millimeters on each of the 3 simultaneous tracings, and the average was calculated. The averages of *r*, *k*, and *ma* for the 8 cases in the different experimental periods were determined and compared. The remaining 4.5 ml. of blood were used for the determination of the prothrombin time by the Link-Shapiro modification[27] of Quick's 1-stage method, on undilute and dilute plasma (12.5 per cent in normal saline).

## RESULTS

### *Prothrombin Times*

The prothrombin time was maintained between 25 and 36.4 seconds, with a mean of 29.5 seconds (undilute), and between 70 and 158.7 seconds, with a mean of 109.3 seconds (dilute). The control times were 15 seconds ± 1 and 40 seconds ± 3, respectively. Six tests were carried out when there was potentiation of effects from the simultaneous effects of 2 anticoagulants with prolonged prothrombin times. This was studied with Marcumar and Tromexan in 2 cases,

Dicumarol and Tromexan in 1, Marcumar and Coumadin in 2, and Coumadin and Marcumar in 1. The prothrombin times ranged from 43 to 105 seconds (undilute), and more than 3 minutes (dilute), in 5 instances. When it was under 60 seconds, the control was obtained by stopping the drug for 2 to 3 days. When it was longer than 60 seconds, vitamin $K_1$ was given in doses between 10 and 30 mg. orally. The sixth case in which potentiation developed was the one with the combination of Dicumarol and Tromexan. In this particular case a change was made from one anticoagulant to the other without a break in therapy. The prothrombin time then became very prolonged to 7 minutes 45 seconds (undilute). Fifty mg. of vitamin $K_1$ were administered and the prothrombin time was repeated 4 hours later. At that time it was 5′3″ and another 60 mg. of vitamin $K_1$ were given. Twenty-four hours later the prothrombin time was 18.6 seconds (undilute). At no time did the patient develop signs or symptoms of bleeding; his urine was normal in all respects. He has been followed in the clinic since (for 3 months) without complications.

Thrombelastograms were also taken in these cases with prolonged prothrombin times. They are not included in the evaluation of the general results in this report, although they are mentioned in the discussion.

Prolongation of the prothrombin time to therapeutic levels was easily obtained with all anticoagulants. There were no accidents.

*Thrombelastographic Results*

The 40 thrombelastographs (5 in each patient) are presented in figure 2 and the complete results appear in table 1. In the controls the reaction time *(r)* measured 18.6 to 26.6 mm., with an average of 22.6 mm. Of the 3 basic thrombelastographic measurements, this one was most frequently and markedly affected by the administration of anticoagulants. Dicumarol was the only coumarin compound that consistently produced an increase of *r* and the other agents increased it in most patients.

In the controls the coagulation time *(k)* measured 10 to 15 mm., with an average of 13.2 mm. Dicumarol and Marcumar again prolonged this measurement more frequently and to a greater degree than the other agents (5 cases each, with an average increase of 1.9 and 1.8 mm., respectively).

In the controls the maximal amplitude (*ma*) measured 47.3 to 59 mm., with an average of 52.5 mm. The changes of this measurement on anticoagulants were very slight.

## Discussion

Coumarin derivatives, when administered to human beings at therapeutic dosage and with a prothrombin time between 25 and 35 seconds, produced moderate changes of the thrombelastogram. These changes were prolongation of the reaction time *(r)*, prolongation of the coagulation time *(k)*, and slight increase of the maximal amplitude (*ma*). The changes in the 3 measurements were very slight (fig. 3). The greatest effect was noted in *r;* however, its prolongation was not very marked and it decreased in 4 of the 32 tracings in anticoagulant periods (1 of Marcumar, 1 of Tromexan, and 2 of Coumadin).

The coagulation time, *k*, was even less affected by the anticoagulants, and although it increased in most cases, it diminished in 13 of the 32 periods (3 of Dicumarol, 5 of Coumadin, 2 of Marcumar, and 3 of Tromexan). In the other instance of Marcumar, *k* remained unchanged.

The maximal amplitude, *ma,* not only did not decrease, but it increased in almost all cases, 25 of the 32. This finding is in agreement with the report by Hartert[14] that the elasticity of the clot *(e)* and, therefore, the maximal amplitude of the tracing (*ma*) is minimally affected by Dicumarol. On the other hand, De Nicola,[20] working with rabbits, found a decrease of *ma* by Dicumarol, Tromexan, and phenylindanedione.

In the patients who presented potentia-

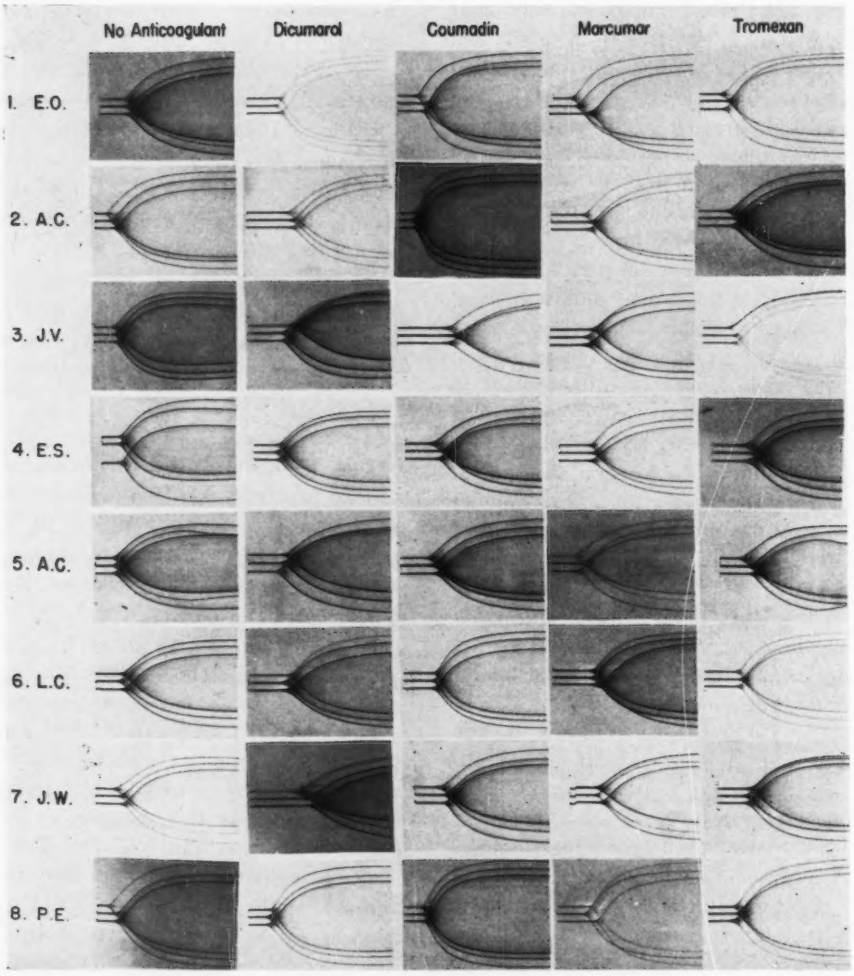


FIG. 2. Thrombelastograms from the 8 patients.

tion of 2 anticoagulants and prolonged prothrombin times, probably the factors of coagulation usually inhibited by these drugs were much more depressed, and probably other factors were also involved.[20] As a result, hemophilic-like patterns were registered in several instances with important prolongation or $r$ and $k$, and decrease of $ma$; the latter, however, increased in some instances. The firmness of the clot probably is reduced in these cases with toxic dosage and the "rupture" of some tracings is then frequently observed (fig. 4). The term "rupture" is used to indicate a "break" or irregularity in the usual curve of the tracing.

The 4 anticoagulants used in this study demonstrated similar action on the thrombelastogram with only small differences. Dicumarol produced the most marked and most consistent response, followed by Marcumar, Tromexan and Coumadin, in that order. One might expect less action from Marcumar, since this coumarin apparently has almost no effect on factor IX (Christmas).[28] Such a difference, however, was not evident in the present study.

TABLE 1.—*Complete Results*

| | No anticoagulant | Dicumarol | Coumadin | Marcumar | Iromexan |
|---|---|---|---|---|---|
| | r* 26.5 | 29 | 23.8 | 26 | 24.5 |
| | k* 14.5 | 11.5 | 10.3 | 14.5 | 15 |
| | ma* 57 | 59.5 | 60.6 | 58.3 | 58.3 |
| | P.T.† 15.0/41.0 | 35.5/137.1 | 33.6/123.2 | 34.5/129.5 | 27.0/88.1 |
| | r 18.6 | 38.5 | 17.5‡ | 36 | 29.8 |
| | k 11 | 15.3 | 9 | 15.5 | 14.6 |
| | ma 56.3 | 56.3 | 65 | 55 | 55 |
| | P.T. 13.7/44.0 | 26.0/70.0 | 30.3/156.2 | 26.2/90.3 | 25.4/88.3 |
| | r 22 | 32 | 41.8 | 32.5 | 24.5 |
| | k 10 | 12.5 | 24.5 | 16.6 | 10.5 |
| | ma 51.3 | 52 | 52 | 49 | 52 |
| | P.T. 17.0/47.2 | 25.2/82.9 | 34.3/132.4 | 26.0/84.4 | 25.0/77.8 |
| | r 20.5 | 24 | 29.8 | 29.5 | 33.8 |
| | k 13 | 12.5 | 14.1 | 16.5 | 15.2 |
| | ma 49 | 50 | 50 | 47.5 | 50.2 |
| | P.T. 14.5/45.0 | 26.7/82.5 | 31.8/158.7 | 32.1/128.0 | 28.8/128.3 |
| 5. | r 26.6 | 29.8 | 30.7 | 34 | 38.2 |
| | k 14.1 | 18 | 15 | 16.3 | 19.3 |
| | ma 50 | 53.6 | 52 | 49.5 | 51 |
| | P.T. 16.0/41.6 | 28.6/95.7 | 31.4/107.6 | 25.5/75.5 | 34.6/134.0 |
| 6. | r 25.1 | 32.1 | 32.5 | 33 | 30.6 |
| | k 15 | 16 | 13.5 | 14.5 | 12.3 |
| | ma 50 | 53.6 | 53.5 | 54 | 55.3 |
| | P.T. 16.5/50.0 | 28.9/116.4 | 28.2/93.5 | 36.4/147.3 | 25.0/80.5 |
| 7. | r 22.5 | 43.3 | 27.3 | 26.6 | 27 |
| | k 15 | 22.5 | 14.3 | 15.3 | 14.6 |
| | ma 47.3 | 48.3 | 51.3 | 48 | 49.3 |
| | P.T. 16.0/42.0 | 25.0/127.0 | 28.5/103.9 | 25.3/84.4 | 25.6/92.0 |
| 8. | r 19 | 22 | 20.6 | 30.5 | 26 |
| | k 11.8 | 11.2 | 8.6 | 10 | 10.8 |
| | ma 59 | 56.5 | 62 | 60 | 61 |
| | P.T. 17.2/49.6 | 34.5/128.6 | 35.0/127.9 | 32.9/120.0 | 29.0/94.6 |

* Average of the 3 tracings in millimeters.
† Undilute and dilute prothrombin time in seconds.
‡ Traumatic puncture.

It is well known that small variations occur from day to day in the thrombelastogram, depending on factors such as diet, stress, and changes in coagulation mechanism that are often inexplicable. The fact that we found slight changes reinforces our opinion that coumarin derivatives have only minimal if any effect on the thrombelastogram.

As compared with these "indirect" anticoagulant agents, heparin has been reported to have a much more marked effect on the coagulogram (fig. 5).[20, 29] This discrepancy is probably due to the different action of the 2 types of anticoagulants on blood coagulation. In fact, heparin may be considered a more complete anticoagulant because it has wider action: antiprothrombin, antithromboplastin, antithrombin (preventing thrombin from reacting with fibrinogen to form fibrin by means of a plasma co-factor), and, finally, preventing the agglutination of platelets.[30]

Coumarin derivatives, on the other hand, have an inhibiting effect mainly on the prothrombin complex (factors VII and prothrombin and with marked overdosage, probably factor V,[2, 5, 9, 10] and secondarily on factors IX and Stuart-Prower.[12, 31]

As the thrombelastogram is closely related to fibrin formation and platelet function, the different action of the 2 groups of antico-

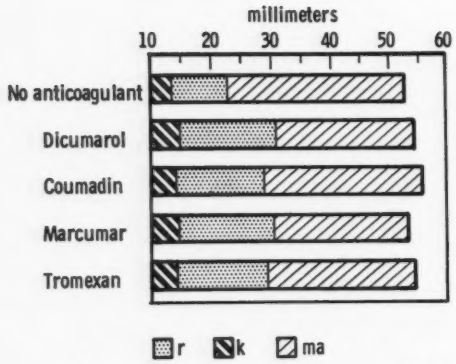


FIG. 3. Average of *r*, *k* and *ma* in millimeters.

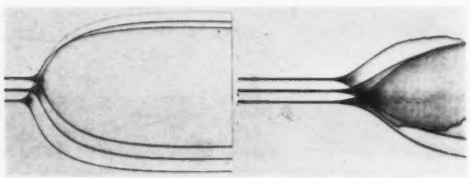

FIG. 4. *Left.* No anticoagulant. Prothrombin time 16.5 seconds. *Right.* Potentiation Dicumarol-Tromexan. Prothrombin time 7.45 minutes. Notice the marked prolongation of *r* and *k*, with rupture of tracing No. 1 before the maximal amplitude could be reached.

agulants on these factors could explain the different behavior of the thrombelastogram.

## CONCLUSIONS

The administration of coumarin derivatives to man was shown to produce definite effects on the thrombelastogram. This action was prolongation of *r and k* times, and increase of *ma*. The effect was slight when average therapeutic dosage of each was administered to the patients and the prothrombin time was maintained within therapeutic levels. The changes were marked, however, when potentiation developed and the prothrombin time was markedly prolonged. The handling of these cases of potentiation served to demonstrate once more that the danger in the use of these drugs is reduced if there is good collaboration between the patient, the physician, and the laboratory, and prompt action is taken to counteract the effects of

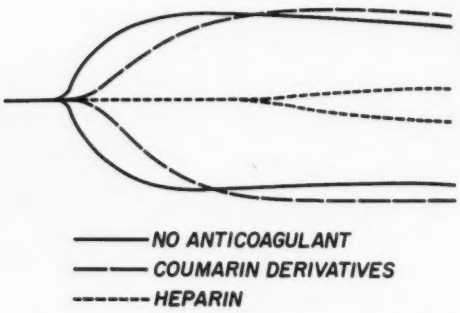


FIG. 5. Scheme showing the different action of coumarin derivatives and heparin on the thrombelastogram. Note the marked prolongation of *r* and *k*, as well as the narrowing of *ma*, following heparin.

excessive dosage. No consistent difference was found among the 4 anticoagulants used in their action on the clot as recorded by the thrombelastogram. Although the thrombelastogram can be used as a complementary study of patients on long-term anticoagulant therapy, it appears that this method is not sensitive enough to the action of coumarin derivatives, and it cannot be substituted for the prothrombin time in the determination of dosage of anticoagulant drugs. The use of whole blood for the thrombelastogram determinations reduces the factors of error and more satisfactory tracings can be obtained than when citrated and recalcified plasma is used.

## SUMMARY

Dicumarol, Coumadin, Marcumar, and Tromexan were administered to 8 patients from the Anticoagulant Clinic of the New York Hospital, who were suffering from different thromboembolic diseases. Simultaneous prothrombin times and thrombelastograms were performed in each patient in the absence of anticoagulants (control values) and during periods of therapy with anticoagulants for a total of 40 tests. Studies were made of the comparative action of these 4 coumarin derivatives on the thrombelastograms. All produced similar changes, namely, slight prolongation of the reaction time *r* and coagulation time *k*, as well as slight increase in

ıe maximal amplitude *ma*. Such changes ere marked, however, when the action of 2 ıticoagulants existed simultaneously and ıe prothrombin time rose to high levels. No nsistent difference could be found among ıese drugs on their action on the clot. The echanism through which "indirect" anti-agulants (coumarin derivatives) and "di-ct" anticoagulants (heparin) act on the lood coagulation was discussed in relation the difference in their effects on the rombelastogram.


### Summario in Interlingua

Al Clinica de Anticoagulantes del Hospital New York, Dicumarol, Coumadina, Marcumar, e Tromexano esseva administrate a 8 patientes con varie morbos thromboembolic. Esseva obtenite, simultaneemente, mesurationes del tempore de prothrombina e thrombelastogrammas pro omne le patientes del serie, (1) in le absentia de anticoagulantes pro establir valores de controlo e (2) durante periodos de therapia con le varie anticoagulantes mentionate. Un total de 40 tal tests esseva executate. Esseva studiate le effectos comparative producite in le thrombelastogramma per le 4 derivatos de coumarina. Omnes produceva simile alterationes, a saper un leve prolongation del tempore de reaction *r* e del tempore de coagulation *k* e etiam un leve augmento del maximo de amplitude *ma*. Tamen, iste alterationes esseva marcate quando le action de 2 anticoagulantes esseva combinate e quando le tempore de prothrombina attingeva un alte nivello. Nulle constante differentia esseva detegibile inter le 4 drogas in lor effecto super le coagulo. Le mechanismo per que anticoagulantes "indirecte" derivatos de coumarina) e anticoagulantes "directe" (heparina) affice le coagulation del sanguine es discutite in relation con le differentias inter lor effectos in le thrombelastogramma.


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In the scientific annals of this great metropolis there is no occasion more memorable than April 16, 1616, when Harvey began his revolutionary teaching. Why the long, the more than Horatian delay, in publishing his great discovery? He knew his day and generation, and even after twelve years of demonstration, which should have disarmed all opposition, we know how coldly the discovery was received, particularly in certain quarters. Harvey, indeed, is reported to have said that he did not think any above forty years of age had accepted the new truth.—William Osler, M.D. *The Importance of Post-Graduate Study.* Lancet, 1900.

# Left Atrial Pressure Pulses in the Presence of Myxoma

*By* ROBERT G. FISH, M.D., TIMOTHY TAKARO, M.D., AND THOMAS CRYMES, M.D.

Findings of transbronchial left heart catheterization in the presence of an atrial myxoma and a normal mitral valve are presented. The genesis and possible significance of unusual differences in contour between high and low left atrial pressure pulses are discussed.

SINCE successful removal of a left atrial myxoma is possible with open-heart surgery, accurate preoperative diagnosis is important. To the best of our knowledge, findings obtained on left heart catheterization in the presence of left atrial myxoma have not been reported. It is the primary purpose of this paper to present and briefly to discuss the left atrial pressure pulses obtained in the presence of a myxoma and a normal mitral valve.

Findings from right heart catheterization alone have shown, in general, evidence only of an obstructive left atrial lesion indistinguishable from mitral stenosis.[1-4] Ellis et al.[5] have noted in addition to elevated pulmonary capillary pressure, cyclic but irregular fluctuations over a wide range in pulmonary artery (50/21 to 90/30) and right ventricle (53/4 to 90/0) pressures in a case of left atrial myxoma, which was later successfully removed. These variations were independent of respiration, alterations in cardiac rhythm, and position. Together with variation of the v-wave peak in the wedge contour ranging from 25 to 40 mm. Hg, these findings were interpreted as evidence of varying degrees of obstruction of left atrial outflow.

The presence of left atrial myxoma may be strongly suspected in the presence of a characteristic combination of clinical features, which has been reported frequently and excellently reviewed by Harvey.[6] In such situation angiocardiography has proved to be a definitive method of diagnosis.[1, 7-9] Although left atrial myxomas have been successfully outlined by venous angiocardiography, this technic is not always successful. Ellis et al.[5] were unable to visualize a suspected and later proved left atrial myxoma by angiocardiography. It is also unfortunate that all left atrial myxomas do not present the clinical picture required to arouse suspicion. The symptomatology and physical findings consequent to a tumor mass in the left atrium will obviously depend on such factors as mobility, size of pedicle, and relationship to mitral valve and pulmonary veins. If a relatively fixed position in relationship to the mitral valve is maintained, the resultant clinical picture is indistinguishable from mitral stenosis. This situation existed in the case to be presented. Unless routine venous angiocardiography is done, these lesions would remain undetected.

Discovery at the time of atriotomy for a planned mitral commissurotomy is the most common method of diagnosis. With discovery of the myxoma the procedure must be abandoned and preparations made for a second thoracotomy and cardiopulmonary bypass. Until technics have advanced to the stage that all mitral valvular surgery is done by an open method, the need for preoperative diagnosis will remain.

If a diagnosis could be established by pressure and pulse contour studies, those obtained in the left atrium would be most ideal for analysis. The following studies, including left heart catheterization, were carried out in a patient mistakenly diagnosed as having pure mitral stenosis. The clinical picture was devoid of any feature that might

From the Cardiopulmonary Laboratory, Veterans Administration Hospital, Oteen, N. C.

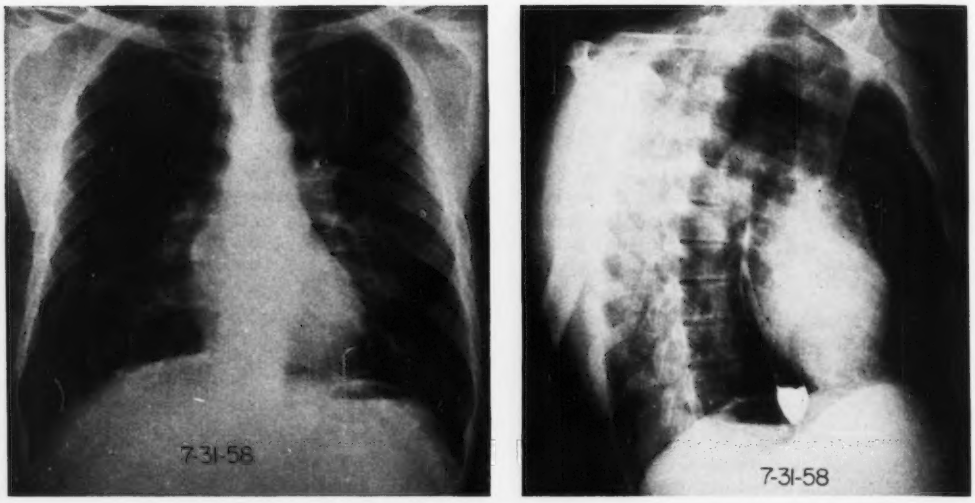


FIG. 1. Posteroanterior and right anterior oblique chest films demonstrating "mitralized" contour and left atrial enlargement.

reasonably arouse suspicion of an atrial myxoma but exploration revealed an entirely normal mitral valve and a large left atrial myxoma.

## CASE REPORT

C.S., a 51-year-old white man, was admitted to the Veterans Administration Hospital, Oteen, North Carolina, on April 18, 1958. Exertional dyspnea had been noted first in December 1956. At this time an apical diastolic murmur was heard and the patient was digitalized. During the ensuing 17 months he noted gradually increasing dyspnea with exercise and occasional episodes of severe paroxysmal dyspnea. These acute episodes were always related to exertion, gradually increased in frequency, and shortly prior to admission were accompanied by streaking hemoptysis. Pedal edema, rest dyspnea, and orthopnea did not occur. There was no history of syncope or respiratory symptoms related to positional changes. A past history of rheumatic fever was not elicited.

Physical examination revealed a blood pressure of 100/70 mm. Hg. The patient was comfortable in the supine position. There was no venous distention or dependent edema. There was no evidence of cardiomegaly or pulmonary congestion and the precordium was quiet. A low-pitched mid and late diastolic murmur merging with the first sound without appreciable presystolic accentuation, and localized at the apex, was present. Neither a mitral opening snap nor an apical systolic murmur was heard. There were no murmurs at the base. A thrill was not felt. The mitral first and pulmonic second sounds were accentuated. These findings were constant on repeated examination and positional change produced no variations. Physical examination was otherwise within normal limits.

Complete blood count, urine analysis, serum proteins and electrolytes, bromsulfalein excretion, antistreptolysin-O titer, C-reactive protein, maximal breathing capacity, timed vital capacity, and serology were all within normal limits or negative.

Fluoroscopic and radiographic examination (fig. 1) revealed left atrial enlargement, straightening of the left heart border, and prominence of the pulmonary artery. Aside from digitalis effect and left atrial hypertrophy the electrocardiogram was not remarkable.

Transbronchial left heart catheterization was performed on April 23, 1958, according to Morrow's technic.[10] Pressure recordings (figs. 2 to 4) were made through a polyethylene catheter with a P23D Statham pressure transducer by means of a cathode ray photographic recording system. Mean left atrial pressures were obtained electronically. Concern over marked hypotension (systolic pressure 60 to 80 mm. Hg) during this procedure led to its termination without determination of cardiac output. At this time an elevated mean left atrial pressure and an obvious ventricular filling gradient without evidence of mitral regurgitation were considered the pertinent findings.

Thoracotomy was performed on May 6, 1958, with a diagnosis of uncomplicated mitral stenosis.

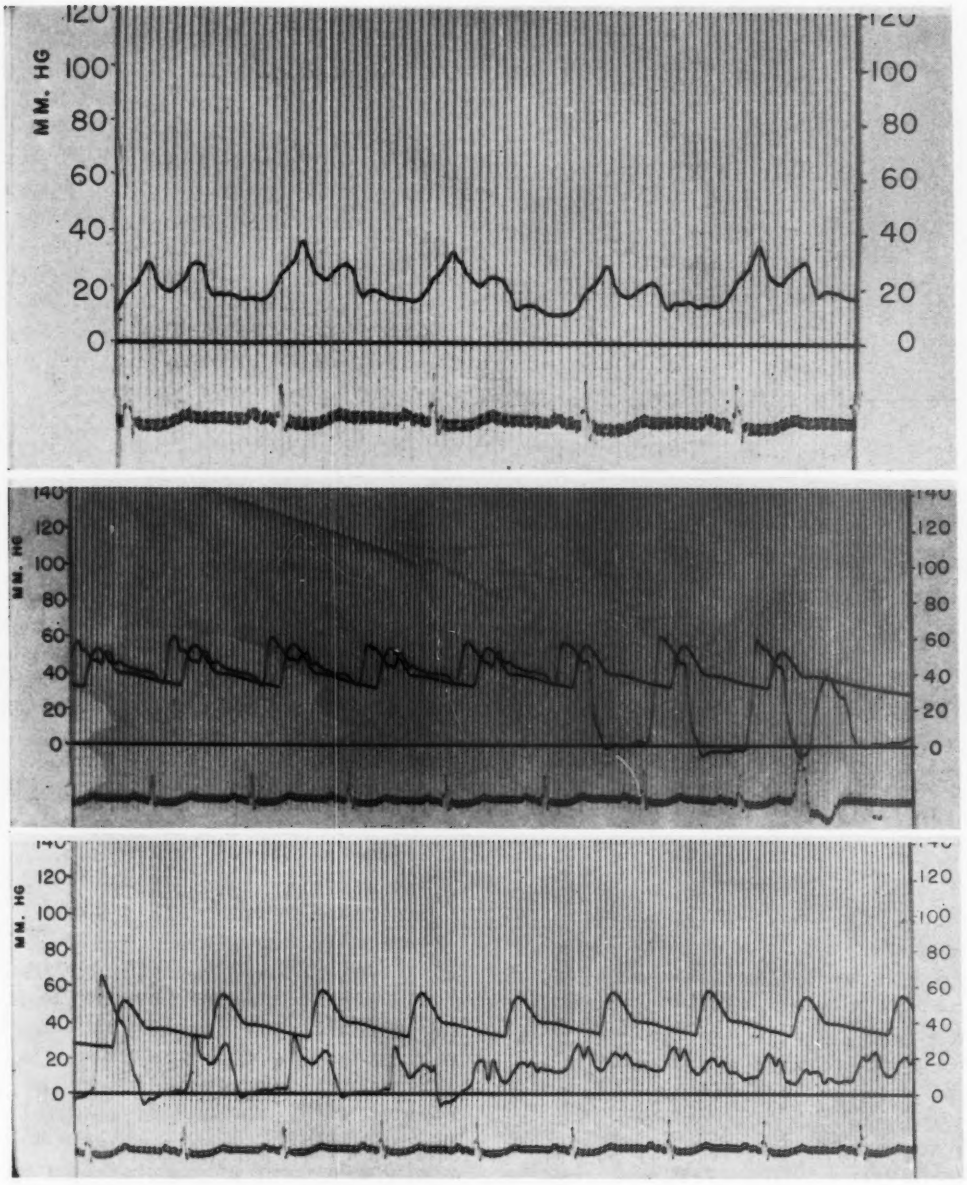


FIG. 2 *Top.* Left atrial pressure pulse obtained immediately after insertion of catheter through the transbronchial needle (high left atrial pressure pulse). *Time lines,* 0.04 second.

FIG. 3 *Middle.* Pressure recordings during withdrawal of catheter from aorta to left ventricle with simultaneous femoral artery pressure recording. *Time lines,* 0.04 second.

FIG. 4 *Bottom.* Pressure recordings during withdrawal of catheter from left ventricle to left atrium (low left atrial pressure pulse). *Time lines,* 0.04 second.

FIG. 5. Gross appearance of resected left atrial myxoma which measured 7.5 by 7 by 4 cm. with a 3 by 4 cm. attachment to the atrial septum.

A firm, smooth, left atrial tumor, attached to the interatrial septum, was encountered. The mitral valve was entirely normal. There was no evidence of regurgitation. In view of the lack of preparation for cardiopulmonary bypass the operation was discontinued.

On August 19, 1958, this tumor (fig. 5) was removed through a right thoracotomy incision during extracorporeal circulation. It weighed 85 Gm. and measured 7.5 by 7 by 4 cm. with a 3 by 4 cm. attachment to the interatrial septum. During atrial closure, however, uncontrollable ventricular fibrillation developed and the patient died.

## DISCUSSION

In the retrospective analysis of these pressure tracings one is struck by certain unusual features. The elevated mean left atrial pressure and the atrioventricular diastolic filing gradient would be expected in the presence of any lesion obstructing left atrial outflow. However, the rapid initial y descent of the left atrial pressure pulse recorded above the tumor (fig. 2), immediately after insertion of the catheter through the Morrow needle, is striking. There is an average drop of 12 mm. Hg in the first 0.08 second of descent, with a mean left atrial pressure of 20 mm. Hg, a pulse rate of 82 per minute, and a normal sinus rhythm. This is followed by a distinct notching and a pressure plateau until atrial contraction.

In an analysis of the left atrial pressure pulse in mitral valve disease with stenosis and insufficiency Morrow et al.[11] found that the ratio of the pressure fall during the first 0.10 second of the y descent to the mean left atrial pressure was of definite value in differentiating the predominant valvular lesion. There was a clear-cut separation of those patients with pure or predominant mitral stenosis. In this group the value of the resultant quotient was less than 0.5. Since the rapid y descent demonstrated in this patient would be anticipated in the presence of a predominantly regurgitant lesion, it is important to point out that no evidence of mitral insufficiency was found clinically or at atrial exploration. This rapid initial y descent would not ordinarily be expected in a purely stenotic valvular lesion and is interpreted as evidence of unobstructed left atrial outflow in early diastole.

Since the transbronchial technic for left heart catheterization was utilized, the catheter may be assumed to lie above the left atrial tumor immediately after insertion through the needle. Comparison of the left atrial pressure pulse at this level with tracings recorded at the time of pull-through from the left ventricle, when the catheter is below or lateral to the tumor, shows sharp differences in contour (fig. 6).

The broad base and short pedicle of this large myxoma would tend to fix it in a relatively constant relationship to the mitral valve. This might explain the lack of variability in physical findings and the absence of historical features suggestive of the presence of an intraatrial mass. While unobstructed early diastolic outflow might be expected, and is apparently demonstrated by the rapid initial y descent, subsequent downward displacement of the tumor into the mitral orifice establishes a ventricular filling pressure gradient. It is postulated that the variation in contour of the high and low left atrial ac complexes is attributable to the difference in relationship of the tip of the catheter and the tumor. It is possible that during circumferential left atrial contraction

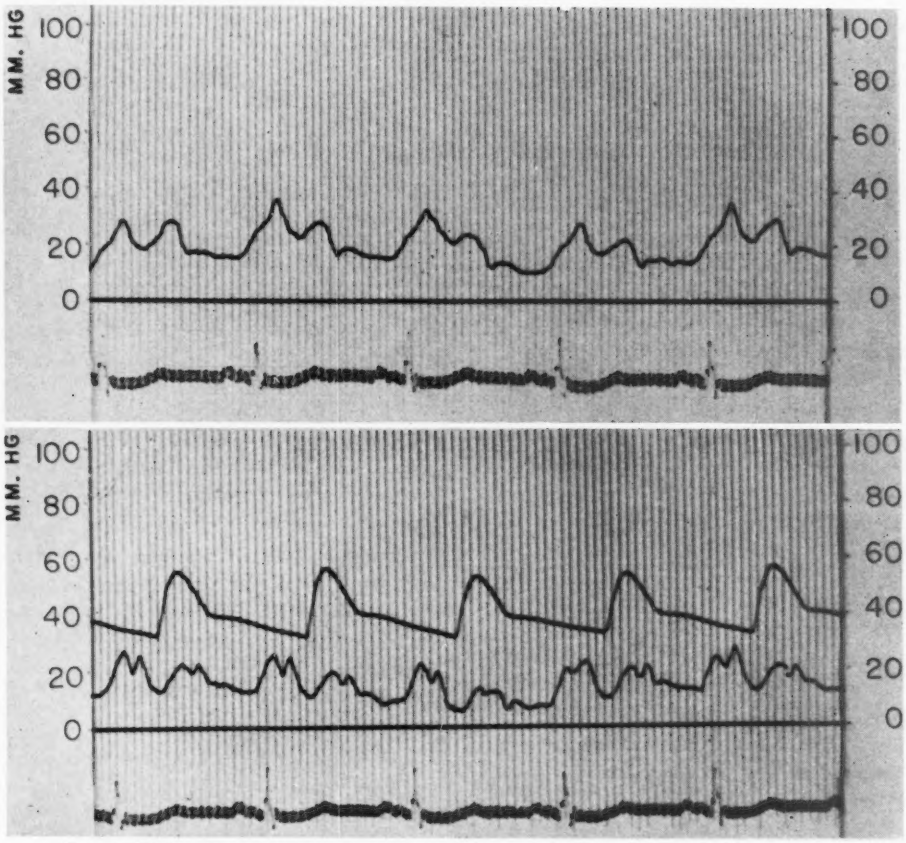


FIG. 6. High left atrial pressure pulse recorded above the myxoma (*top*) and low left atrial pressure pulse recorded below this tumor (*bottom*). Note the marked difference in contour.

a 2-chamber atrium was in effect created with different pressure relationships above and below the tumor. Thus the contour of the pressure pulse recorded with the catheter tip below the myxoma differs from that recorded above (fig. 7).

It is important to point out that this study was carried out in a patient assumed to have mitral stenosis. The clinical features often associated with left atrial myxoma were lacking. It is not our intention to imply that left heart catheterization or selective left atrial cardioangiography is the most desirable method of study in those cases where the existence of a myxoma may be suspected. The danger of dislodging emboli from a friable myxoma by needle insertion or high-

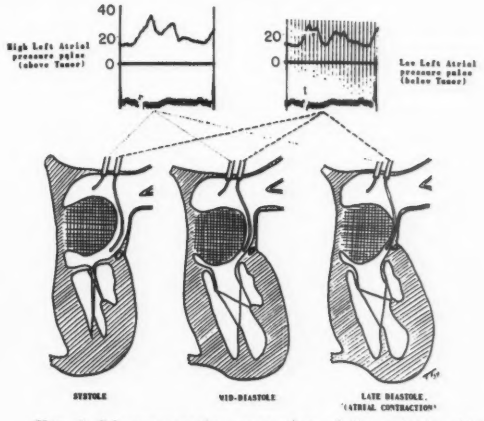


FIG. 7. Diagrammatic conception of the relationship of catheter tip to myxoma (above and below the tumor) during cardiac cycle with corresponding atrial pressure pulses.

velocity dye injection makes these procedures unsafe. Venous angiocardiography is the diagnostic procedure of choice in this situation.


## Summary

Left atrial pressure pulses obtained in the presence of an unsuspected left atrial myxoma are presented. The clinical picture was that of uncomplicated mitral stenosis. In addition to an elevated mean left atrial pressure and ventricular filling gradient they are characterized by a brief initial period of apparently unobstructed left atrial outflow and by differences in contour between high and low left atrial recordings. These dissimilarities are thought to reflect the different pressure relationships that occur above and below the tumor.

## Summario in Interlingua

Es presentate pulsos de tension sinistro-atrial obtenite in le presentia de un non-suspicite myxoma sinistro-atrial. Le aspecto clinic esseva illo de non-complicate stenosis mitral. A parte un elevate valor medie del tension sinistro-atrial e un gradiente de replenation ventricular, constatationes characteristic esseva un breve periodo initial de apparentemente non obstruite effluxo sinistro-atrial e differentias de contorno inter registrationes sinistro-atrial alte e basse. Es opinate que iste dissimilaritates reflecte le differente relationes de tension que occurre supra e infra le tumor.


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# Visualization of the Left Branch of the Human Atrioventricular Bundle

*By* HERMAN N. UHLEY, M.D., AND LAURENCE M. RIVKIN, M.D.

Visualization of the atrioventricular node and bundles of His in the human heart has been very difficult in the past, so much so that the very existence of specialized conducting tissue in man has been questioned. The authors present a simplified technic permitting visualization of the left bundle of His that facilitates studies in this area.

THE atrioventricular bundle in the human heart has been extremely difficult to visualize. Methods of dissection have been described, but the procedure is largely limited to the hands of experts.[1] A simple method for visualizing the bundle system would be of invaluable aid to all persons interested in the conduction system. It is the purpose of this paper to demonstrate a technically simple means by which the left branch of the conduction system may be readily visualized in the human heart.

## METHODS

The use of Lugol's solution to bring out glycogen in histologic studies is well known[2] and iodine staining to demonstrate the conduction system in dogs has been described.[3] The technic employed consists of swabbing the endocardial surface of the human heart with cotton soaked in aqueous Lugol's iodine solution. The single essential point is that the hearts must be examined shortly after death (within 1½ hours), for the reaction depends upon the glycogen present in the conduction system and glycogen disappears at a very rapid rate after death.[4] Within 2 to 5 minutes after contact with the Lugol's solution the left bundle appears just beneath the endocardial surface of the septum as a series of bluish radiations. Washing with water removes excessive Lugol's solution and the bundle stands out more clearly. The hearts were photographed and then fixed in absolute alcohol. Sections of the blue-appearing areas were stained with Best's carmine to demonstrate the presence of muscle fibers rich in glycogen.

## RESULTS AND DISCUSSION

Figures 1 and 2 are photographs of the septal surface of the left ventricle. Although photographic reproduction fails to produce as much contrast as is apparent on direct visualization, a band of tissue can be distinguished extending downward from the posterior leaf of the aortic valve. About one third of the way down the fibers divide into 2 branches. The anterior branch continues through the trabecular network to the posterior papillary muscle. The left branch lies close to the endothelial surface and during application of the Lugol's solution one notes that a more intense color appears if the endothelium is carefully removed. Since the main bundle and most of the right bundle are deeper structures, they are not visualized with superficial staining. In addition to the time factor, the type of disease process may influence the rate of depletion of the bundle glycogen and consequently the intensity of the stain. The best results were obtained in diseases in which death came suddenly, i.e., myocardial infarctions (not involving the main branches of the conduction system) in contrast to uremia and carcinoma. Perhaps the appearance of bundle-branch block in the electrocardiogram taken during an agonal state may be related to glycogen alteration in the bundles.

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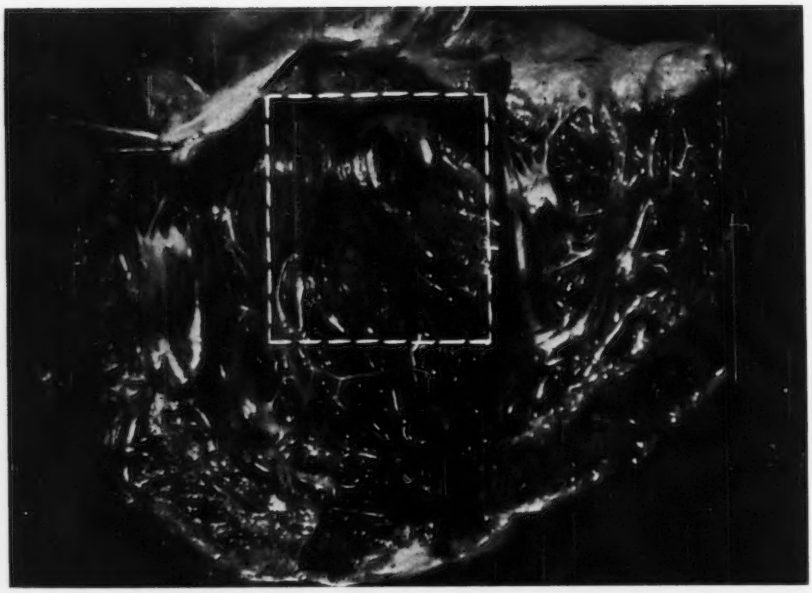

FIG. 1. Left ventricle of a human heart depicting the stained left branch of the bundle of His and its ramifications.

FIG. 2. Upper portion of the left ventricular septum showing the left bundle as it divides into anterior and posterior branches.

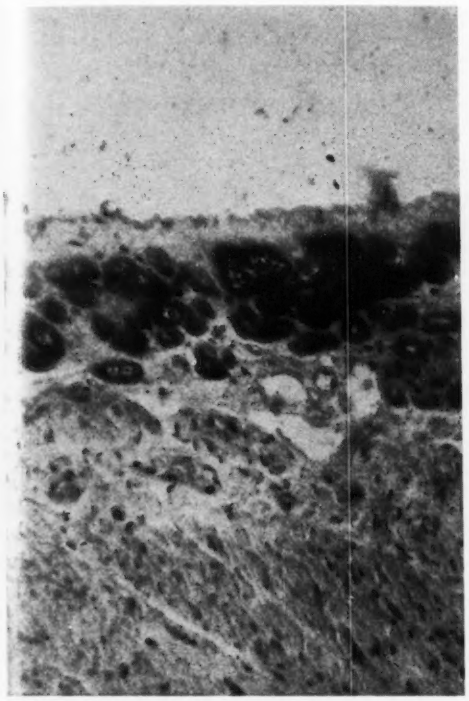

FIG. 3. Section from a stained area of the upper portion of the left ventricular septum (Best's carmine). Dark fibers denote the high concentrations of glycogen in the subendocardial fibers.

Figure 2 shows a section taken from the left bundle in the upper one third of its course stained with Best's carmine for glycogen. Glycogen-rich bundle fibers are present near the subendocardial surface. It is apparent that this simple procedure of application of Lugol's solution for visualization of the left branch of the conduction system affords an excellent opportunity for studying the gross anatomy of this specialized tissue.


## SUMMARY

The direct application of Lugol's solution to the endocardial surface of a fresh heart (within 1½ hours after death) from a patient who did not have a glycogen-depleting illness, provides an excellent means of grossly identifying the left bundle of the conduction system. The technic has obvious applicability in electrocardiographic and clinical-pathologic correlations.



## ACKNOWLEDGMENT

The authors wish to express their thanks to Dr. Gerson R. Biskind and Dr. Alvin E. Lewis for their valuable assistance.



## SUMMARIO IN INTERLINGUA

Le application directe de solution de Lugol al superficie endocardial de un corde fresc—intra un hora e medie post morte—ab un patiente non afficite de un morbo a depletion de glycogeno provide un medio excellente pro le identification macroscopic del fasce sinistre in le systema de conduction. Le technica ha obviemente applicationes in establir correlationes inter constatationes electrocardiographic e clinico-pathologic.


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# Plasma Norepinephrine Response to Tilting in Essential Hypertension

*By* Roger B. Hickler, M.D., James T. Hamlin III, M.D., and Roe E. Wells, Jr., M.D.

A significant increase in the plasma concentration of norepinephrine on tilting 19 normal subjects from the horizontal to 60° upright is described. Evidence that this represents an increased neuroadrenergic activity to maintain cerebral circulation despite the peripheral pooling of blood has previously been reported. When 9 subjects with severe essential hypertension were similarly tilted, the rise in plasma norepinephrine concentration was insignificant. This may indicate a diminished neuroadrenergic activity in essential hypertension due to compensatory reflexes from the baroreceptor regions.

THERE is sufficient evidence to indicate that essential hypertension is not due to increased neuroadrenergic activity.[1-3] The demonstration of elevated levels of urine norepinephrine excretion in only 16.4 per cent of 500 hypertensive patients is additional evidence.[4] Conversely, there is suggestive evidence of a diminished neuroadrenergic activity in essential hypertension. Gellhorn, in his monograph "Autonomic Imbalance and the Hypothalamus" cites the classical investigation of earlier workers to support the general thesis that a "fall of the blood pressure leads to increased sympathetic and adrenal discharges, and that a rise of blood pressure causes increased parasympathetic discharges."[5] Sundin demonstrated a 3- to 4-fold increase in urine norepinephrine excretion on tilting normal subjects from the horizontal to an upright position.[6] In hypertensive subjects the rise was only about 60 per cent. He suggested that the chronically elevated pressure in the baroreceptor areas in essential hypertension leads to a state of diminished endogenous norepinephrine production.

A previous report from this laboratory described the measurement of a significant increase in the concentration of plasma norepinephrine within minutes of tilting normal subjects from the horizontal to 60° upright.[7] A failure to detect a significant rise in subjects with postural hypotension was also described. In order to investigate further the thesis of a diminished neuroadrenergic activity in essential hypertension, this method was extended to hypertensive subjects.

## Method

Nineteen normotensive subjects (resting diastolic pressure below 90 mm. Hg), with a mean age of 59 years (range 29 to 80), served as a control group. These were compared with 9 subjects with essential hypertension (resting diastolic pressure above 100 mm. Hg), with a mean age of 60 years (range 43 to 73). Thirteen subjects formed an "intermediate" group (resting diastolic pressure 90 to 100 mm. Hg). All were ambulatory and none was on medication. The usual clinical and laboratory methods were used to eliminate patients with an identifiable cause for their hypertension. After a 30-minute rest in the supine position on a standard tilt table, each subject was tilted 60° upright for a 30-minute period. Brachial blood pressures were recorded every minute by auscultation and a standard aneroid blood pressure cuff. Pulse rate was determined by counting the radial pulse. Venous samples were drawn through an inlying needle with stylet in the right antecubital vein during the control period and at 2.5, 5, 10, 20, and 30 minutes after tilting upright. The samples were heparinized and the plasma separated by centrifugation and stored at —18 C. The Aronow and Howard modification[8] of the Weil-Malherbe and Bone method[9] was used for subsequent determination of norepinephrine concentration. While nonhormonally active hydroxyphenol compounds in the plasma may also be detected by this fluor-

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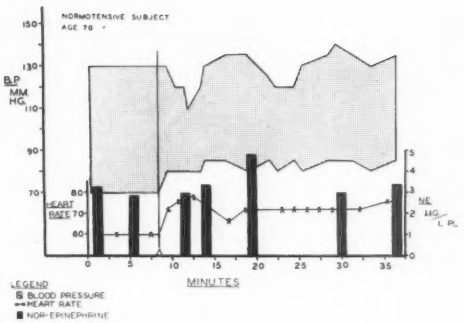
TABLE 1.—*Effect of Essential Hypertension on the Plasma Norepinephrine Response to Tilting*

| Group | No. of subjects | Plasma norepinephrine—mean (μg./L. plasma) Control | Peak | Increment | p |
|---|---|---|---|---|---|
| Normotensive (Diastolic pressure 90 mm. Hg) | 19 | 3.2±1.3 | 5.1±1.3 | 1.9±1.1 | <0.01 |
| "Intermediate" (Diastolic pressure 90-100 mm. Hg) | 13 | 3.6±1.2 | 5.1±1.4 | 1.5±1.0 | <0.01 |
| Hypertensive (Diastolic pressure >100 mm. Hg) | 9 | 3.3±1.3 | 4.2±1.8 | 0.9±0.8 | >0.2 |

metric method, any abrupt changes on tilting are considered to be due to the labile hormonal fraction. The normal range for plasma norepinephrine in this laboratory in the resting subject is 1.5 to 5.5 μg. per L. The repeatability of the method is ± 10 per cent, so that changes of 1 or more micrograms per liter plasma between control and peak norepinephrine concentration after tilting are considered to be significant.

## Results

Figure 1 demonstrates a typical response in a normotensive subject, age 70. The blood pressure was well maintained after tilting. The rise in diastolic pressure and pulse rate are probably manifestations of the increased neuroadrenergic activity attending the orthostatic stress. The slight fall in norepinephrine concentration between the first and second control samples prior to the tilt probably represents an approach to a baseline level on resting horizontally on the tilt board. After tilting to 60° the norepinephrine concentration rose, reached a peak after 10 minutes, and then returned toward the control level. The increment is taken as the difference between the last control sample just prior to the tilt and the peak value after the tilt. In this instance the increment was 1.8 μg. per liter plasma. In the 19 normotensive subjects studied the mean increment was 1.9 ± 1.07 μg., representing a significant rise over the control levels ($p < 0.01$). In only 2 instances was the rise less than 1 μg. (0.1 and 0.8 μg.).



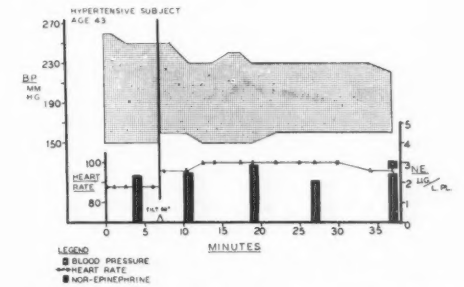




FIG. 1 *Top.* Tilt-table study in a normal subject, showing a significant rise in the plasma concentration or norepinephrine following the tilt.

FIG. 2 *Bottom.* Tilt-table study in a subject with severe essential hypertension, showing an insignificant rise in the plasma concentration of norepinephrine following the tilt.

Figure 2 demonstrates the response in a hypertensive subject, age 48. There was a maximum fall in systolic pressure of 30 mm. Hg associated with a relatively small rise in norepinephrine concentration of only 0.7 μg. per L. plasma after 30 minutes of tilting. In 9 hypertensive subjects studied the mean increment was 0.9 ± 0.77 μg., representing an insignificant rise over the control levels ($p > 0.2$). In the "intermediate" group (13 subjects with a diastolic pressure 90 to 100 mm. Hg) the mean increment was 1.5 ± 1.02 μg., a significant rise ($p < 0.01$) of a degree intermediate between the normotensive and distinctly hypertensive groups (table 1). It is notable that the mean control values for the 3 groups showed no significant difference

TABLE 2.—*Effect of Age on the Plasma Norepinephrine Response to Tilting in Normotensive Subjects*

| Subjects | No. of Subjects | Plasma norepinephrine—mean (μg./L. plasma) | | | |
|---|---|---|---|---|---|
| | | Control | Peak | Increment | *p* |
| Young (Mean age 35) | 7 | 2.8±1.0 | 5.1±1.3 | 2.3±1.3 | <0.01 |
| Old (Mean age 73) | 12 | 3.5±1.3 | 5.2±1.4 | 1.8±0.9 | <0.01 |

TABLE 3.—*Effect of Essential Hypertension on the Hemodynamic Response to Tilting*

| Group | Mean change in pulse (beats/min.) | Mean change in systolic pressure (mm. Hg) | Mean change in diastolic pressure (mm. Hg) |
|---|---|---|---|
| Normotensive (15 subjects) | +12 | −16 | +6 |
| Hypertensive (9 subjects) | +22 | −29 | +3 |

TABLE 4.—*Effect of Age on the Hemodynamic Response to Tilting in Normotensive Subjects*

| Subjects | No. of subjects | Mean change in pulse (beats/min.) | Mean change in systolic pressure (mm. Hg) | Mean change in diastolic pressure (mm. Hg) |
|---|---|---|---|---|
| Young (mean age 35) | 7 | +19 | −10 | +13 |
| Old (mean age 73) | 12 | +9 | −19 | +1 |

(normotensive group, 3.2 μg.; "intermediate" group, 3.6 μg.; hypertensive group, 3.3 μg.). Thus the relatively insignificant rise in the hypertensive group could not be related to a higher baseline.

Age difference could not account for the difference, since the mean ages of the normotensive and the hypertensive groups were both 59 years. To determine the effect of age per se on the norepinephrine response to tilting, independent of hypertension, the 19 normotensive subjects were divided into 2 groups: 7 subjects under age 60 (mean of 35 years) and 12 over age 60 (mean of 73 years) (table 2). Both groups showed a significant rise: mean rise of 2.3 ± 1.3 μg. for the young ($p < 0.01$) and 1.8 ± 0.9 μg. for the old ($p < 0.01$). The difference in mean increase between the young and old groups was not significant ($p > 0.3$).

The hemodynamic data were analyzed by comparing the pulse rate and systolic and diastolic pressure just prior to the tilt with the maximum change observed following the tilt (table 3). In the hypertensive group the mean increment in the pulse rate was almost double that for the normotensive group; the diastolic pressure rise was only half and the systolic pressure fall was almost double that of the normotensive group.

An analysis of the effect of aging, independent of hypertension, was accomplished by comparing the pressure and pulse response in the 7 young and 12 old normotensive subjects. Table 4 illustrates the smaller pulse and diastolic pressure rise and the greater systolic pressure fall in the old group, consistent with the vascular "brittleness" of advancing age.

## DISCUSSION

These results suggest that in essential hypertension there is a diminished responsiveness of the sympathetic nervous system. Previous studies have shown that bilateral adrenalectomy does not modify the norepinephrine excretion in urine[10] or the plasma norepinephrine response to tilting.[7] The changes therefore must represent a difference between normotensive and hypertensive subjects in the rate of release of norepinephrine (over rate of destruction) by the sympathetic nerve endings.

Subjects with autonomic hypofunction resulting in postural hypotension have also shown a diminished plasma norepinephrine response to tilting.[7] Such a similarity between hypertensive subjects and subjects with postural hypotension might seem at face value to be paradoxical. An analysis in this laboratory of the plasma norepinephrine and hemodynamic response to tilting in 6 subjects with postural hypotension is compared with the

sults of the present study (table 5). It can seen that the subjects with hypertension id postural hypotension in comparison with ie normotensive subjects have a relatively flat'' plasma norepinephrine response, asso-ated with a poorer maintenance of systolic id diastolic blood pressure against a gravi-tional stress. The changes are not so marked essential hypertension, and it is suggested iat the degree of sympathetic unresponsive-ess is not so severe.

The rate of renal excretion of a parenteral lt load demonstrates another similarity be-ween essential hypertension and postural ypotension. Studies have demonstrated an xaggerated natriuresis associated with paren-eral saline administration in essential hyper-ension[11] and in postural hypotension[12] as ompared with normal subjects. The factor in common may be a diminished sympathetic regulatory mechanism on renal salt conserva-tion. Indirect evidence of the possible impor-tance of the neuroadrenergic system on so-dium excretion may be cited. Norepinephrine infusion has been shown to cause sodium re-tention.[13] Dibenzyline infusion into the renal artery in dogs with experimental valvular heart lesions has been shown to augment so-dium excretion.[14]

Evidence is accumulating of a hyperreac-tive response of the vasculature of the hyper-tensive subject to parenteral administration of catecholamines.[15-17] This may be compara-ble to the postsympathectomy subject in whom increased reactivity to administered pressor substances is characteristic of the state of diminished sympathetic innervation.[18, 19] With this in mind the finding of postural ypotension in 50 per cent of subjects with heochromocytoma may seem less surpris-ng.[20] The high level of circulating pressor nine and concomitant hypertension may tually obtund the responsiveness of the uroadrenergic system, particularly when lled upon to respond quickly to an abrupt ange in body position.

It is possible that in the labile phase of sential hypertension, normotensive periods

TABLE 5.—*Effect of Essential Hypertension and Postural Hypotension on the Plasma Norepinephrine and Hemodynamic Response to Tilting*

| Group | Mean increment in plasma norepinephrine (μg./L. plasma) | Mean change in pulse (beats/min.) | Mean change in systolic pressure (mm. Hg) | Mean change in diastolic pressure (mm. Hg) |
|---|---|---|---|---|
| Normotensive (19 subjects) | 1.9 | +12 | −16 | +6 |
| Hypertensive (9 subjects) | 0.9 | +22 | −29 | +3 |
| Postural hypotensive (6 subjects) | 0.5 | +19 | −81 | −30 |

are maintained in the face of the basic hypertensive process by virtue of a reflexly diminished neuroadrenergic activity. Situations which then acutely evoke the release of pressor amine may act upon a vasculature rendered hyperresponsive by a chronically diminished endogenous norepinephrine production, resulting in transient periods of hypertension. The hypertensive process, at this point, could be regarded as incompletely compensated.

## SUMMARY

An insignificant rise in the venous concentration of norepinephrine was found on tilting 9 hypertensive subjects from the horizontal to 60° upright. A significant rise was found when 19 normotensive subjects were similarly stressed.

The hypertensive group showed a greater fall in systolic pressure and a smaller rise in diastolic pressure following this orthostatic stress. This was comparable to the more striking fall in both systolic and diastolic pressures in subjects with autonomic hypofunction resulting in postural hypotension.

It is concluded that in essential hypertension there may be a diminished reflex responsiveness of the neuroadrenergic system. This could represent an unsuccessful homeostatic mechanism against the hypertensive state.

## SUMMARIO IN INTERLINGUA

Un augmento insignificative del concentration venose de norepinephrina esseva consta-

tate post bascular 9 subjectos hypertensive ab le decubito horizontal a un inclination de 60 grados in alto. Un augmento significative esseva trovate in 19 subjectos normotensive post lor exposition al mesme typo de stress.

Le gruppo hypertensive monstrava un plus grande reduction del tension systolic e un plus miere augmento del tension diastolic post le describite stress orthostatic. Isto esseva comparabile al plus frappante reductiones del tension tanto systolic como etiam diastolic que es vidite in subjectos con hypofunction autonome resultante in hypotension postural.

Es concludite que in hypertension essential il existe possibilemente un reducite responsivitate reflexe del systema neuroadrenergic. Isto representarea un non-successose mechanismo homeostatic contra le stato de hypertension.

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# Successful Repair of Sinus of Valsalva-Left Atrial Fistula

*By* JEROME HAROLD KAY, M.D., ROBERT M. ANDERSON, M.D., REUBEN R. LEWIS, M.D., AND MARTIN REINBERG, M.D.

DISSECTING sinus of Valsalva–left atrial fistula is a rare lesion. An extensive search of the literature from 1935 to 1958 has failed to reveal a similar case. There are many reports of rupture of a sinus of Valsalva into the right side of the heart. Three of these reports have been made by Chipts,[1] Fowler and Bevil,[2] and Hirschboeck.[3] Lillehei, Stanley, and Varco,[4] and Morrow, Baker, Hanson, and Mattingly[5] have reported the repair of these right-sided lesions. Various reports mention the possibility of rupture of the sinus of Valsalva to the left atrium, but no reference has been found of a specific case of this type. It is believed that this is the first case of sinus of Valsalva–left atrial fistula reported and successfully repaired.

## CASE REPORT

A 39-year-old housewife had been well until April 1958, when she began to notice gradually increasing weakness, dizziness, and exertional dyspnea. She became faint and dizzy on bending. She had 2 rather severe episodes of faintness but there was no complete loss of consciousness. She continued to do her housework but rested frequently because of fatigue and mild dyspnea. She had no complaints of chest pain, chest tightness, cough, or hemoptysis. There had been no weight loss or any complaints referable to other symptoms.

Past illnesses included measles, mumps, chickenpox, and whooping cough in childhood. She had a mild episode of rheumatic fever at the age of 14. An automobile accident in her youth caused only minor injuries. She denied the use of alcohol, tobacco, or any drugs.

Physical examination revealed an alert young woman in no acute discomfort. The blood pressure was 120/70, and the pulse was 74. Her heart had normal rhythm. The second pulmonic sound was split and slightly accentuated, and no murmurs or thrills were present. The apex beat was at the fifth intercostal space in the midclavicular line, and no abnormal precordial thrust was present. The liver was not enlarged, there was no pedal edema, and the dorsalis pedis pulses were strong. X-ray taken July 3, 1958 (fig. 1*A*), showed a 6 by 6 cm. mass at the posterolateral aspect of the left cardiac border. Comparison with the films taken 2 years previously at another hospital revealed marked increase in the size of the mass during that time.

Right heart catheterization with angiocardiography failed to determine whether the mass was intracardiac or extracardiac. Satisfactory pressure and blood samples from the pulmonary artery, right heart, and venae cavae revealed no evidence of a right-to-left or left-to-right shunt. Electrocardiograms showed nonspecific T-wave changes, the T wave being inverted in leads I and $aV_L$ and flattened in $V_5$ to $V_6$.

On July 18, 1958, exploration through a left posterolateral thoracotomy was done in anticipation of finding an extracardiac tumor. The left atrium was found to be markedly distended and tense from the presence of a hard, nonpulsating mass, which seemed to underly the entire anterior wall of the left atrium. The mass pressed on and distorted the left circumflex coronary artery.

The chest was closed, and removal of the intracardiac mass was postponed until such time as it could be done with the aid of a cardiopulmonary bypass. The mass was thought to be a myxoma of the left atrium.

On September 9, 1958, the chest was entered by a median sternotomy with an extension into the left third intercostal space. The Kay-Anderson heart-lung was used to maintain cardiopulmonary bypass for 1 hour. During this time an incision was made into the left atrial wall overlying the mass. A cavity 7 cm. in diameter was entered, and several large clots were evacuated (fig. 2). A jet of bright red blood was found to be spurting from the base of this cavity. This jet originated from an opening 7 mm. in diameter at the base of the aorta and

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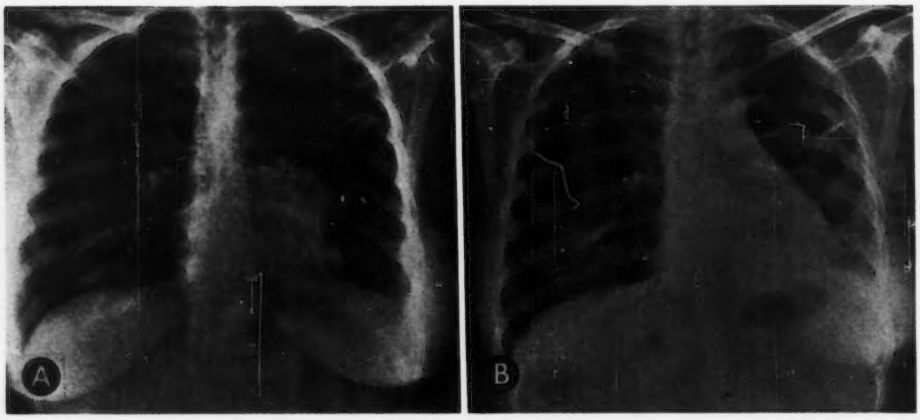


FIG. 1. *A*. X-ray taken July 3, 1958. *B*. X-ray 2 months after operation.

was synchronous with the arterial pump. Upon occlusion of the jet, blood was seen to ooze into the cavity through several small pinpoint openings, which were found to connect with the lumen of the left atrium. The intramural mass had nearly compromised the left atrial cavity and had partially occluded the mitral opening. The left atrium was entered through a second atrial incision superior and posterior to the first. The mitral valve was found to be normal, as was the entire lining of the left atrial chamber. The primary fistula opening at the base of the sinus of Valsalva of the aorta was closed with 2 figure-8 sutures of no. 2-0 silk. The secondary atrial openings were also closed. The sides of the dissected atrial wall were then re-appropriated with consecutive rows of interrupted no. 2-0 silk to obliterate the aneurysmal cavity. After the repair the left atrium appeared to be normal in size and configuration.

The postoperative course was uneventful. Two months later, the patient had none of her preoperative dyspnea, fatigue, and dizziness, and her electrocardiogram was normal. The T-waves were now upright in lead I and a$V_L$ and of normal contour in $V_3$ to $V_8$. The chest x-ray showed a normal cardiac configuration (fig. 1*B*).

## DISCUSSION

In this patient there was an absence of the usual signs found in a fistula of the sinus of Valsalva. The absence of a large pulse pressure, murmur, and thrill was due to the small blood flow through the fistula. This small flow was due to the tiny secondary openings

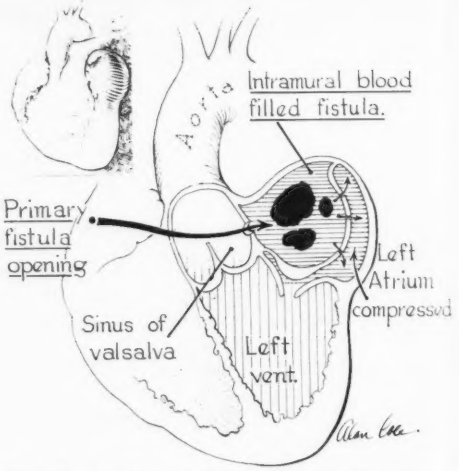


FIG. 2. Drawing depicting rupture of coronary sinus into the left atrial wall with further dissection into the left atrium. The aneurysmal dilatation of the left atrial wall caused partial obstruction of the mitral valve orifice.

into the left atrium. Distortion of the left atrial wall with blockage of the mitral orifice and distortion of the coronary arteries probably accounted for the patient's symptoms. Venning[6] reported on myocardial infarction associated with electrocardiographic changes in cases of fistula of the sinus of Valsalva. The return to normal of the electrocardiogram is of interest in this case.

SUMMARY

An unusual dissecting sinus of Valsalva-left atrial fistula with successful repair is reported. This lesion was repaired by open heart surgery with the utilization of a heart-lung machine.

SUMMARIO IN INTERLINGUA

Es reportate un caso inusual de fistula inter dissecante sino de Valsalva e atrio sinistre. Le lesion esseva reparate, a bon successo, in chirurgia a corde aperte con le utilisation de un machina cardio-pulmonar.

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Such is indeed the intimate relation of the affective faculties with the movements of the heart that most philosophers regard that organ as the seat of the passions and that in all languages the word heart is frequently employed as synonymous with sentiment, affection, soul or passion. Whether this be true or not, it is *incontestable* that all the active passions powerfully modify the movements of the heart. Some of them excite, others augment and some convert into violent palpitations, others distend or momentarily release them, and somtimes permanently.

In this respect, we might say, that of all our modes of expression, the heart is the most faithful and is the interpreter of all our most sincere emotions.—R. J. BERTIN. *Treatise on the Diseases of the Heart and Great Vessels.* Edited by J. Bruillard. Translated from the French by Charles W. Chauncy, M.D. Philadelphia, Carey, Lea and Blanchard, 1833, Introduction XLV.

## SPECIAL ARTICLE

# The "Tough Case" of Bacterial Endocarditis

*By* ERNEST JAWETZ, M.D., PH.D.

Many cases of bacterial endocarditis can now be cured rapidly and easily. However, there remains a group of patients in whom the eradication of the cardiac infection presents great problems. Some principles of treating these "tough cases" of endocarditis are outlined by means of illustrative patients. Stress is placed on early diagnosis, isolation of the etiologic microorganism, determination of bactericidal antibiotics or combinations, and use of the serum bactericidal test to establish an adequate dosage regimen.

THE treatment of bacterial endocarditis consists of 2 parts: the eradication of the bacterial infection, and the management of the cardiac disability and other organ dysfunctions developing in the course of the disease. Only the first of these aspects, the treatment of the bacterial infection is considered here. Excellent and exhaustive reviews of the general antimicrobial therapy of bacterial endocarditis have been published recently.[1-4] It would be futile therefore to recapitulate the entire subject. Instead, a few points of importance in the management of the difficult case are illustrated.

The advent of penicillin transformed bacterial endocarditis from an interesting, but uniformly fatal entity into an infection that was often cured without much difficulty. The eradication of *Streptococcus viridans,* the commonest etiologic agent, has become a simple matter in most cases. There remains, however, a group of patients in whom, for one reason or another, the eradication of the infection presents the physician with unusual problems. A few such illustrative cases are presented here.

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The key to the successful treatment of any case of bacterial endocarditis is early recognition and accurate etiologic diagnosis. The physician must maintain an exceedingly high index of suspicion to include bacterial endocarditis in the differential diagnosis of vague or puzzling complaints. After all, bacterial endocarditis does not always present the full range of typical signs and symptoms. The patient might show nothing more than tiredness or anemia with a mild elevation of temperature, or, conversely, he might present the picture of an overwhelming sepsis without signs pointing to cardiac involvement. The earlier the physician thinks of bacterial endocarditis, the more promptly he can undertake the isolation of the etiologic agent and begin treatment.

In bacterial endocarditis, perhaps more than in any other infection, cure depends on the identification of the infecting microorganism and its availability for laboratory study. Thus a determined effort must be made in every case to culture the blood (and occasionally the bone marrow) promptly and repeatedly. Even in extremely severe, fulminating cases it is well to defer the administration of antimicrobial agents for at least a few hours in order to obtain several blood cultures. When the patient is not acutely ill, it is fully justified to obtain 1 or 2 cultures on each of 3 to 5 days before beginning treatment.[5] The recovery of the etiologic bacteria permits a

nuch sounder guess as to the best drugs to e used than if the etiology is uncertain, and, bove all, provides direct laboratory support or devising a satisfactory treatment regimen. s soon as the requisite number of cultures as been obtained, treatment may be started n the basis of the "best guess," to be modi- ed when laboratory findings become avail- ble. In about 10 per cent of cases of bacterial ndocarditis, an organism cannot be cultured ven with exhaustive and competent efforts. n those few instances the choice and dosage f antibiotics must continue to be based on uesswork and past experience. In virtually ll other cases, it should be founded upon the esults of laboratory examinations.

When requested to determine the antibiotic sensitivity of a microorganism, most hospital laboratories report results based on the "disk test." In many diseases, the antimicrobial activity of a drug estimated by the "disk test" gives a valuable prediction of the probable effect of that drug in the patient. In bacterial endocarditis, however, the results of the disk test are not only without value, but, on the contrary, may be entirely misleading. The conventional disk test only estimates the ability of a drug to inhibit the growth of microorganisms. Such inhibitory action is of great therapeutic value in many diseases—but *not* in endocarditis. The antibacterial defenses of the host, which are effective in many other illnesses, are unable to eradicate the microorganisms from their protected location within vegetations. Drugs which are predominantly bacteriostatic (e.g., sulfonamides, tetracyclines, chloramphenicol, erythromycin, novobiocin) generally do not cure bacterial endocarditis if employed alone.[2, 3, 6] Cure requires drugs that are rapidly bactericidal for the etiologic microorganism. Laboratory tests suitable to guide therapy in bacterial endocarditis must evaluate the bactericidal action of single or combined drugs. Conventional "disk tests" cannot do that, but several technics for the estimation of bactericidal action are available.[7–10] In "simple" cases of bacterial endocarditis caused by *Strep. viridans,* which is generally very sensitive to penicillin, this deficiency of the disk test may not be apparent. If penicillin is selected as the drug of choice on the basis of experience as well as the marked inhibition reported in the disk test, it may be forgotten that penicillin is also a very effective bactericidal agent. But in cases of endocarditis caused by penicillin-resistant bacteria, the reliance on the "disk test" may lead to the selection of entirely improper antibiotics. An example is shown in figure 1.

This 64-year-old man with endocarditis had many positive blood cultures for hemolytic *Staphylococcus aureus.* Repeated "disk tests" were employed for the selection of drugs. They revealed that the organism was not inhibited by penicillin, but was markedly inhibited by tetracycline, erythromycin, novobiocin, oleandomycin, and streptomycin. The patient was treated with each of these drugs in succession. Each time he showed some temporary clinical improvement, but either during therapy or shortly after its cessation he relapsed clinically and bacteriologically. Permanent cure was obtained only when bactericidal drug combinations (tetracycline + streptomycin + bacitracin) in appropriate concentrations were employed.

The first rule, then, is the selection of bactericidal drugs for treatment. Admittedly certain drugs are rapidly bactericidal in vitro yet fail to eradicate the apparently susceptible bacteria in the patient. To be effective in bacterial endocarditis the bactericidal drugs must diffuse well into the vegetations and must not be bound by tissue or components of the thrombotic lesion. The inability to reach the infecting organisms may account for the frequent failure of polymyxin B in endocarditis caused by Pseudomonas.[11]

As a general rule, however, diffusible antibiotics, which are rapidly bactericidal in vitro for a given organism, tend to cure endocarditis caused by that organism, if administered in adequate dose for a sufficient period. The dosage can be roughly estimated from the amount of drug required to kill the organism

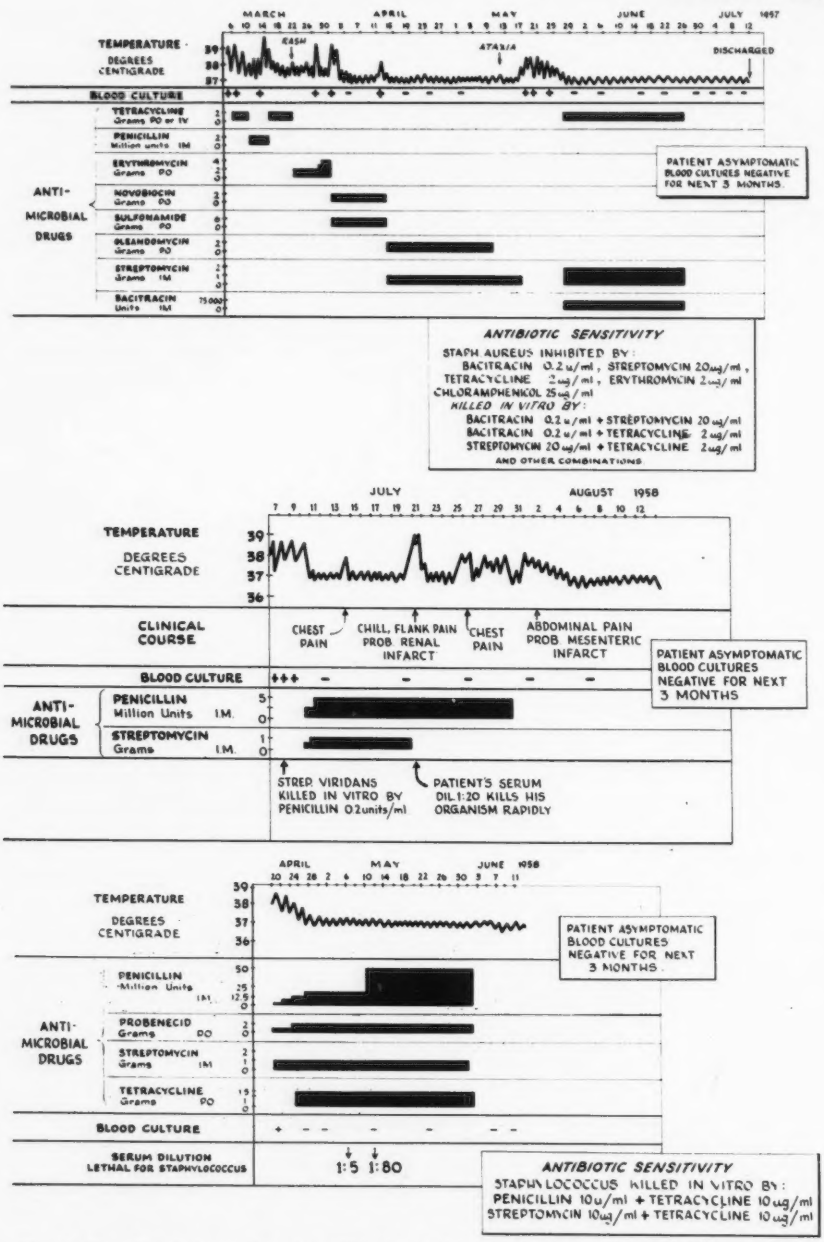


FIG. 1 *Top.* Staphylococcal endocarditis in a 64-year-old man. The misleading results of "disk tests" in guiding antibiotic therapy. (*Reproduced, by permission, from Arch. Int. Med. Jawetz, E., 103: 289, 1959.*)

FIG. 2 *Middle. Streptococcus viridans* endocarditis in a 39-year-old man. The serum bactericidal test indicates adequate antibiotic therapy in spite of a stormy clinical course. (*Reported by permission of Dr. W. Atchley.*)

FIG. 3 *Bottom.* Staphylococcal endocarditis in a 39-year-old man, with slow initial response to therapy. Serum bactericidal test used in adjusting drug dosage to "secure" levels. (*Reported by permission of Dr. M. Sokolow.*)

n vitro under standardized conditions.[7, 9] But hat if the patient's response leaves much to e desired? The physician's anxiety over a atient's stormy course may tempt him to dd or withdraw drugs at frequent intervals nd thus interfere with effective chemotherpy. Once a definitive regimen of antibacterial herapy has been decided upon, the physician hould not alter it without compelling reasons. Reassurance concerning adequacy of antibitic dosage may be derived—in addition to terile blood cultures—from an evaluation of he bactericidal power in vitro of the patient's erum under therapy against his own infectng organism.[12] This point is illustrated in igure 2.

This 39-year-old man had a "simple" bacterial endocarditis on a rheumatic mitral valve. The *Strep. viridans* isolated from his blood stream was rapidly killed in vitro by penicillin 0.2 unit per ml. Accordingly a treatment regimen was outlined consisting of penicillin, 5 million units daily intramuscularly for 20 days, and streptomycin, 1 Gm. daily intramuscularly for the first 10 days. The patient's initial response was satisfactory and his blood cultures promptly became sterile. However, he exhibited repeated febrile episodes with severe pains pointing to embolic events in lungs and kidney. Was he receiving adequate amounts of antibiotics? The physician's concern was allayed by finding that the patient's serum, diluted 1:20, killed his own organism rapidly in the test tube. In spite of a stormy course, treatment was continued and terminated as planned. The patient required anticoagulant therapy but his bacterial infection was eradicated and he recovered completely. Embolic phenomena occur before, during, and even after successful antibiotic therapy. Their occurrence is disquieting and, at times, leads to tragic results. Yet by themselves they should not induce the physician to abandon a well-conceived treatment plan. Similarly the frequent occurrence of drug fever must not be permitted to interfere with an established treatment regime.

The patient shown in figure 3 also had an unsatisfactory initial response to treatment. He was a 39-year-old man who had recovered from 2 previous attacks of bacterial endocarditis due to *Strep. viridans* during the past 9 years. His present attack was due to a hemolytic *Staph. aureus* implanted on an insufficient aortic valve, and had failed to respond to 1 month's intensive treatment at another hospital. Laboratory examination indicated that his organism could be killed in vitro by several combinations. After treatment with laboratory-selected drug combinations was begun (fig. 3), blood cultures became sterile but defervescence was slow and the patient did not feel well. His serum killed his staphylococcus in a dilution of 1:5, but not 1:10. This was considered an inadequate safety margin and consequently the dose of penicillin was increased from 20 to 50 million units daily. There was immediate, marked, subjective improvement as the serum became bactericidal in a 1:80 dilution. After 3½ weeks of therapy at that level bacteriologic cure was established.

Different laboratories, using slightly different technics for the assay of the bactericidal activity of serum of the patient under treatment, have slightly different standards of what serum dilution reflects drug levels adequate for cure of endocarditis. However, within the framework of its own experience with the serum bactericidal test[3, 6] each laboratory can give valuable guidance to the antibiotic treatment of "tough cases" of endocarditis. While reliable data are available indicating what average blood levels may be expected from different time-dose schedules of antibiotics in the usual dose range, the combined antibacterial effect of several drugs at very high dose levels is difficult to predict and must be assayed directly in the patient's serum.

One of the difficult problems in bacterial endocarditis concerns the treatment of the hyperacute, destructive lesion, often associated with staphylococci. It is particularly important to treat such patients with the utmost speed and vigor, with use of bactericidal combinations of usually not less than 3 drugs in very large doses. An example is given in

figure 4. This 55-year-old man was entirely well until 8 days before entry, when he developed a mild "flu-like" illness with fever and diarrhea. His physician treated him for 4 days with chloramphenicol but there was only slight improvement. He then noted the presence of a heart murmur and the development of petechiae on the lower extremities. He suspected bacterial endocarditis and referred the patient to the University hospital because there was a history of an allergic reaction to benzathine penicillin 1 year earlier. On admission to the hospital the patient was acutely ill, lethargic, with occasional shaking chills and a fever of 39 C. He had not received antibiotics for 2 days. His lower extremities were covered with petechial hemorrhages, and there were petechiae also on his eyelids, conjunctivae, and palate. He had splinter hemorrhages under several nails. A harsh grade-III systolic murmur was heard over the entire precordium. The white blood cell count was 16,000 with 85 per cent polymorphonuclear leukocytes, the corrected erythrocyte sedimentation rate was 34 mm. per hr., and 2 blood cultures taken within 2 hours of admission yielded (the next day) more than 300 colonies per ml. of hemolytic, coagulase-positive *Staph. aureus*.

The clinical diagnosis upon admission was acute bacterial endocarditis, probably caused by staphylococci. If the patient's life was to be saved, it was essential to start effective treatment immediately. It was reasoned that (a) the staphylococcus might be penicillin-sensitive because the patient and his family had not had contact with a hospital environment; (b) the earlier slight response to chloramphenicol suggested that the organism might be sensitive to that drug; (c) streptomycin at times enhances the bactericidal effect of penicillin against certain cocci. Because of these considerations the patient was started on combined therapy with chloramphenicol, penicillin, and streptomycin as soon as blood cultures had been taken. In view of the history of a penicillin reaction in the past, this drug was administered with several precautions. At first a skin test with 100 units penicillin O was performed, which gave no immediate reaction. Then 1,000 units of penicillin O were given intramuscularly, again without local or systemic response. An hour later an intravenous infusion of penicillin O was begun, together with intravenous benadryl 100 mg., and cortisone injection was held in readiness. Penicillin was tolerated then and subsequently without any difficulty. Laboratory examinations for antibiotic sensitivity (fig. 4) supported the empiric choice of drugs. After a few days of continued lethargy and high fever, the patient defervesced and improved gradually. His serum was bactericidal for his staphylococcus in dilutions of 1:40 or more. After 5 weeks of antimicrobial treatment all antibiotics were stopped and follow-up examinations for 4 months indicated bacteriologic cure. The patient suffered a brief episode of congestive heart failure 2 months after the end of antimicrobial therapy. This was attributed to violent exercise, a high salt intake, and discontinuing digitalis intake against medical advice. There was prompt response to conventional therapy and to date no evidence of significant valve destruction has appeared. The course of this patient illustrates the need for immediate treatment with very large amount of bactericidal antibiotics chosen initially on the basis of reasoning, and later by laboratory test. It also shows that if penicillin is the drug of greatest life-saving potential, it can often be administered in spite of a history of past allergic reactions. Finally, it suggests that treatment might be extended for more than 4 weeks in staphylococcal endocarditis, although the optimal period of antibiotic therapy in such cases is not known.

Among the "tough cases" of endocarditis it is necessary at the present time to include patients who acquired their microorganism from a hospital environment. Such bacteria are notoriously resistant to the more widely used antibiotics and their eradication is extraordinarily difficult. While the principles of selecting bactericidal drugs in appropriate doses, and assaying the bactericidal potency of serum during treatment, are the same as

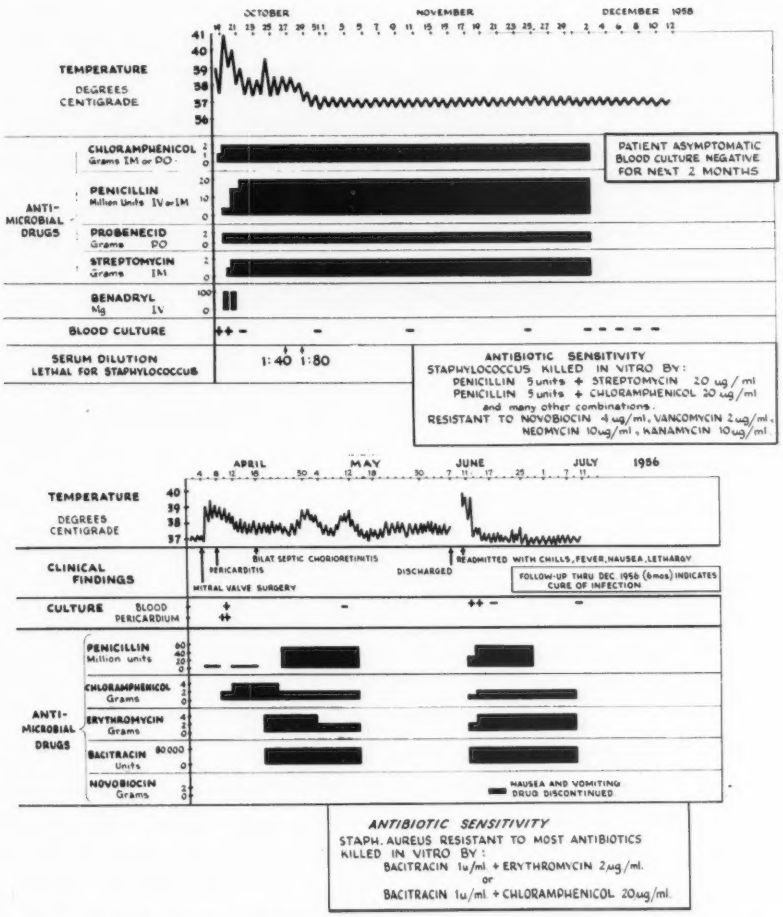


FIG. 4 *Top.* Acute endocarditis due to hemolytic *Staphylococcus aureus* in 55-year-old man. Immediate massive antibiotic therapy based on "best guess." Drug selection confirmed by laboratory result. *(Reported by permission of Drs. H. D. Brainerd and D. Mitchell.)*

FIG. 5 *Bottom.* Acute endocarditis, pericarditis and chorioretinitis due to hemolytic *Staphylococcus aureus* introduced during mitral valvulotomy in a 44-year-old man. *(Reproduced, by permission, from Arch. Int. Med., Jawetz, E., 103: 289, 1959).*

outlined above, markedly toxic antimicrobial substances often must be employed. In the use of full systemic doses of such drugs as bacitracin, neomycin, kanamycin, vancomycin, or ristocetin the risk of serious toxic side effects must be weighed against the risk of treatment failure in a disease that is uniformly fatal unless the infection can be eradicated. An example is given in figure 5.

This 44-year-old man had a very tight mitral stenosis that seriously embarrassed cardiac function. After thorough study a mitral valvulotomy was performed. In the course of surgery a "hospital staphylococcus" was apparently introduced which resulted in sepsis with endocarditis, pericarditis, and multiple abscesses at other sites. In vitro the staphylococcus appeared highly resistant to commonly used antibiotics but could be killed by combinations of bacitracin with erythromycin or chloramphenicol. The patient was treated with these drugs as shown in figure 5 (with

the addition of penicillin on the basis of hope rather than factual evidence). The nephrotoxic effects of bacitracin were carefully evaluated at frequent intervals. The patient responded after an initial stormy course but became psychotic, so that treatment had to be stopped prematurely. After some weeks of remission his mental status improved but the infection relapsed. When re-treated for 4 full weeks with the same combination of drugs (but with the omission of penicillin for part of the time), the patient was cured to enjoy the benefits resulting from the surgical procedure. With experience in the use of toxic antibiotics, it is often possible to minimize their toxic effects and employ them for the protracted periods necessary to eradicate both cardiac and metastatic infection. Laboratory guidance is essential to select optimal drugs and doses and to keep careful check on the toxic side effects. Obviously every effort must be made to drain collections of pus.

The above description may give the impression that rational selection and use of drugs invariably succeeds in curing patients with "difficult" forms of endocarditis. Unfortunately this is not true. While we firmly believe that in every patient the rational sequence outlined above should be followed, occasional failures occur. Most commonly they are associated either with the presence of metastatic infection (e.g., lung abscesses), which cannot be drained adequately, or with damage to valves or myocardium, which leads to cardiac failure.

It would likewise be misleading to claim that only the rational selection of drugs can ever lead to the cure of endocarditis. In an occasional patient, infected with a particularly resistant organism we have observed repeated failure with laboratory-guided rational therapy, yet unexplained success when additional drugs—of doubtful activity against the particular organism—were employed.[13] Such multiple antibiotic "shotgun" therapy must be accepted for the desperately ill patient with acute endocarditis awaiting laboratory studies, and for the rare case where carefully selected bactericidal antibiotic combinations have failed to eradicate the infection. However, these exceptional situations should not detract from the validity of the rational approach.

## Summary

The advent of penicillin has converted bacterial endocarditis from a uniformly fatal to a readily curable disease in most instances. However, the treatment of some cases still presents great difficulties. Efforts must be made to obtain the etiologic organism in every patient.

The frequently employed laboratory tests for bacterial sensitivity to antibiotics ("disc test") are meaningless and misleading in endocarditis. They measure bacteriostatic drug effects, whereas in endocarditis bactericidal antibiotics must be employed. By the use of suitable examinations, the laboratory can suggest the single or combined drugs and doses necessary to kill the organisms. The adequacy of the antibiotic dosage regimen may be evaluated (in addition to sterile blood cultures) by the bactericidal action of the patient's serum against the organism previously isolated from his blood stream.

When the endocarditis is caused by drug-resistant bacteria, bactericidal antibiotic combinations may have to include toxic drugs for prolonged treatment periods. The risk of employing the drug has to be weighed in each case against the risk of possible treatment failure due to its omission. Using these principles we have been fortunate in curing a high proportion of "tough cases" of bacterial endocarditis.

## Acknowledgment

I wish to express my gratitude to Drs. W. Atchley, H. D. Brainerd, D. Mitchell, F. Solomon, and M. Sokolow for permission to participate in the treatment of the patients used here as examples and to report their course. Many helpful discussions with these and other colleagues are acknowledged with appreciation.

## Summario in Interlingua

Depost le advento de penicillina, endocarditis bacterial ha cessate esser un condition uniformemente mortal e es hodie un morbo prestemente curabile in le majoritate del casos.

Tamen, in certe casos le tractamento remane difficilissime. On debe effortiar se a obtener le organismo etiologic in omne patiente individual.

Le frequentemente empleate tests laboratorial pro determinar le sensibilitate bacterial a antibioticos ("test a discos") ha nulle valor e es mesmo illudente in le caso de endocarditis. Illos mesura effectos bacteriostatic del droga, sed in endocarditis antibioticos de fortia bactericida debe esser empleate. Super le base de appropriate examines, le laboratorio pote proponer le droga o combination de drogas e le dosage necessari pro occidar le organismos. Le adequatia del dosage de antibiotico pote esser evaluate—a parte le obtention de sterile culturas de sanguine—per observar le action bactericida del sero del patiente contra le organismo previemente isolate ab su circulation de sanguine.

Quando le endocarditis es causate per bacterios pharmacoresistente, il pote devenir necessari includer in le combination de antibioticos bactericida un supplemento de drogas toxic e administrar los durante prolongate periodos de tempore. Le risco representate per le uso del drogas toxic debe esser ponderate in omne caso individual contra le risco de un possibile fallimento del tractamento si illos es omittite. Per le uso de iste principios nos ha habite le bon fortuna de curar un alte procentage de "casos recalcitrante" de endocarditis bacterial.

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## SPECIAL ARTICLE

# The Earliest Record of Sudden Death Possibly Due to Atherosclerotic Coronary Occlusion

*By* WALTER L. BRUETSCH, M.D.

The sudden death of an Egyptian nobleman is portrayed in the relief of a tomb from the Sixth Dynasty (2625-2475 B.C.). Since there is indisputable evidence from the dissections of Egyptian mummies that atherosclerosis was prevalent in ancient Egypt, it was conjectured that the sudden death might have been due to atherosclerotic occlusion of the coronary arteries.

IT MAY be presumptuous to assume that an Egyptian relief sculpture from the tomb of a noble of the Sixth Dynasty (2625-2475 B.C.) may suggest sudden death possibly due to coronary atherosclerosis and occlusion.

Much of the daily life of the ancient Egyptians has been disclosed to us through well-preserved tomb reliefs. In the same tomb that contains the scene of the dying noble, there is the more widely known relief "Netting Wildfowl in the Marshes."[1] The latter sculpture reveals some of the devices used four thousand years ago for catching waterbirds alive. It gives a minute account of this occupation, which in ancient Egypt was both a sport and a means of livelihood for the professional hunter.

The relief (fig. 1), entitled "Sudden Death," by the Egyptologist von Bissing[2] represents a nobleman collapsing in the presence of his servants. The revelant part of the explanatory text, as given by von Bissing, follows (translation by the author):

> The interpretation of the details of the theme is left to the observer. We must attempt to comprehend the intentions of the ancient artist who sculptured this unusual scene. In the upper half (to the right) are two men with the customary brief apron, short hair covering the ears, busying themselves with a third man, who obviously has collapsed. One of them, bending over him, has grasped with both hands the left arm of the fallen man; the other servant, bent in his left knee, tries to uphold him by elevating the head and neck, using the knee as a support. Alas, all is in vain. The movement of the left hand of this figure, beating against the forehead, seems to express the despair; and also in the tightly shut lips one can possibly recognize a distressed expression. The body of the fallen noble is limp. . . . Despite great restraint in the interpretation, the impression which the artist tried to convey is quite obvious. The grief and despair are also expressed by the figures to the left. The first has put his left hand to his forehead. (This gesture represents the Egyptian way of expressing sorrow.) At the same time he grasps with the other arm his companion who covers his face with both hands. The third, more impulsively, unites both hands over his head. . . . The lord of the tomb, Sesi, whom we can identify here, has suddenly collapsed, causing consternation among his household.
>
> In the section below (to the left) is shown the wife who, struck by terror, has fainted and sunk to the floor. Two women attendants are seen giving her first aid. To the right, one observes the wife, holding on to two distressed servants, leaving the scene. . . .

von Bissing mentions that the artist of the relief must have been a keen observer of real life. This ancient Egyptian scene is not unlike the tragedy that one encounters in present days, when someone drops dead of a "heart attack." The physician of today has almost no other choice than to certify the cause of such a death as due to coronary occlu-

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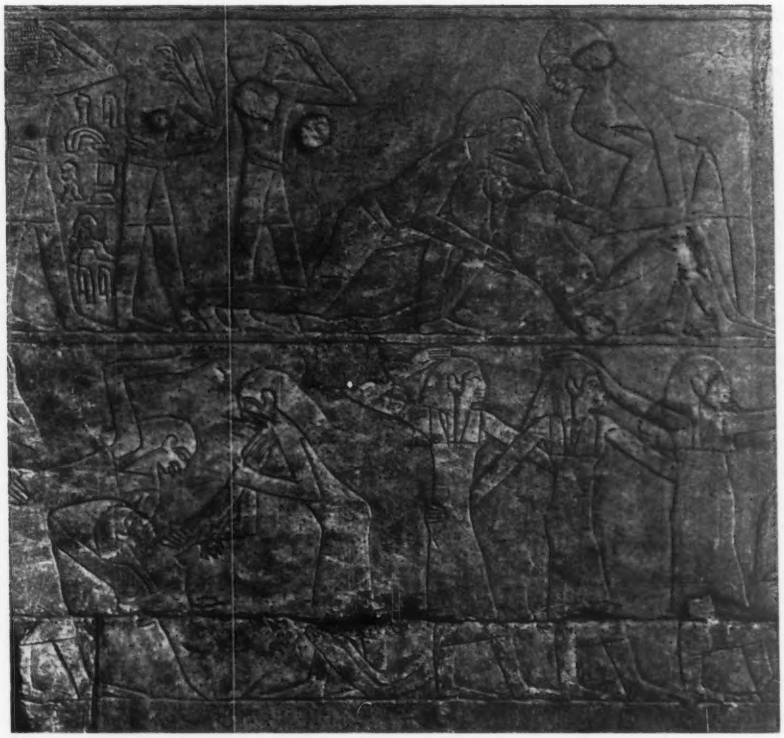

FIG. 1. Tomb relief depicting the sudden death of an Egyptian nobleman (*upper right*), who collapses in the midst of his family. Two servants busy themselves with the dead noble, while others show their grief with the characteristic gesture—hands to the forehead—expressing sorrow in ancient Egypt. *Below*, the wife, overcome by emotion, has fainted and sunk to the floor. She is being attended by two women who are trying to revive her. To the *right*, the wife, holding on to two servants, is being led from the scene. Tomb of Sesi at Sakkara. (Sixth Dynasty 2625-2475 B.C.). *(Reproduced from Plate 18B, "Plötzlicher Tod" (Sudden Death), in F. W. von Bissing: Denkmäler Ägyptischer Sculptur. Plates I, 1-57, München, F. Bruckmann, 1914.)*

sion or thrombosis, unless the patient was known to have been afflicted with rheumatic heart disease or with any of the other more rare conditions which may result in sudden death.

## ATHEROSCLEROSIS AMONG THE ANCIENT EGYPTIANS

The most frequent disease of the coronary arteries, causing sudden death, is atherosclerosis. What evidence is available that atherosclerosis was prevalent in ancient Egypt?

The first occasion to study this condition in peoples of ancient civilizations presented itself when the mummified body of Menephtah (approx. 1280-1211 B.C.), the reported "Pharaoh of the Hebrew Exodus" from Egypt was found. King Menephtah had severe atherosclerosis. The mummy was unwrapped by the archaeologist Dr. G. Elliot Smith, who sent a piece of the Pharaoh's aorta to Dr. S. G. Shattock of London (1908). Dr. Shattock was able to prepare satisfactory microscopic sections which revealed advanced aortic atherosclerosis with extensive depositions of calcium phosphate.[3]

This marked the beginning of the important study of arteriosclerosis in Egyptian mummies

by Sir Marc Armand Ruffer, of the Cairo Medical School (1910-11).[4, 5] His material included mummies ranging over a period of about 2,000 years (1580 B.C.-525 A.D.).

The technic of embalming in the days of ancient Egypt consisted of the removal of all the viscera and of most of the muscles, destroying much of the arterial system. Often, however, a part or at times the whole aorta or one of the large peripheral arteries was left behind. The peroneal artery, owing to its deep situation, frequently escaped the embalmer's knife. Other arteries, such as the femorals, brachials, and common carotids, had persisted.

In some mummies examined by Ruffer the abdominal aorta was calcified in its entirety, the extreme calcification extending into the iliac arteries. Calcified plaques were also found in some of the larger branches of the aorta. The common carotid arteries frequently revealed patches of atheroma, but the most marked atherosclerotic alterations were in the arteries of the lower extremities. The common iliac arteries were not infrequently studded with calcareous plaques and in some instances the femoral arteries were converted into rigid tubes. In other mummies, however, the same arteries were near normal.

What is known as Mönckeberg's medial calcification was also observed in some of the mummified bodies. In a histologic section of a peroneal artery, the muscular coat had been changed almost wholly by calcification. In one of Ruffer's photographic plates, a part of a calcified ulnar artery is shown. The muscular fibers had been completely replaced by calcification.

In the aorta, as in present days, the atherosclerotic process had a predilection for the points of origin of the intercostal and other arteries. The characteristics and the localization of the arterial lesions observed in Egyptian mummies leaves little doubt that atherosclerosis in ancient times was of the same nature and degree as seen in today's postmortem examinations.

As to the prevalence of the disease, Ruffer ventured to say that the Egyptians of ancient times suffered as much as modern man from arterial lesions, identical with those found in our times. Ruffer was well qualified to make this statement having performed many necropsies on modern Egyptians, Moslems, and other people of the Middle East. In going over his material and examining the accompanying photographic plates of arteries, one can have little doubt that what Ruffer had observed in Egyptian mummies represented arteriosclerosis as it is known today.

Although the embalming left no opportunity to examine the coronary arteries in mummified bodies, the condition of the aorta is a good index of the degree of atherosclerosis present elsewhere. In individuals with extensive atherosclerosis of the aorta, there is almost always a considerable degree of atherosclerosis in the coronary arteries. If Ruffer's statement is correct that the Egyptians of 3,000 years ago were afflicted with arteriosclerosis as much as we are nowadays, coronary occlusion must have been common among the elderly population of the pre-Christian civilizations.

Furthermore, gangrene of the lower extremities in the aged has been recognized since the earliest records of disease. Gangrene of the extremities for centuries did not undergo critical investigation until Cruveilhier (1791-1873) showed that it was caused by atherosclerotic arteries, associated at times with a terminal thrombus.


## Summary

The record of a sudden death occurring in an Egyptian noble of the Sixth Dynasty (2625-2475 B.C.) is presented. Because of the prevalence of arteriosclerosis in ancient Egyptian mummies there is presumptive evidence that this incident might represent sudden death due to atherosclerotic occlusion of the coronary arteries.

## Summario in Interlingua

Es presentate le documentation de un morte subitanee in un nobile egyptian del sexte dynastia (2625 a 2475 a.C.). A causa del preva-

latia de arteriosclerosis in mumias del ancian Egypto, il ha provas presumptive que iste incidente representa un morte subite causate per occlusion atherosclerotic del arterias coronari.

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**Pre-Harveian Doubts of Galenic Doctrine**

The interest in theology had apparently always been smoldering not too far below the surface of Servetus' mind, and with his additional work on Bibles and religious commentaries it now blazed forth to become the major force in the last years of his life. Although he had previously failed to convince either Zwinglian or Lutheran authorities, nevertheless he seems to have believed that there was yet the possibility of winning over Calvin to his views on the reform of Christianity. Through the aid of a bookseller as intermediary, Servetus entered into correspondence with the Genevan reformer, requesting his explanation on various theological points and then characteristically proceeding to denounce such explanations as Calvin sent. It was, of course, futile from the beginning. Servetus, dogmatic to the end, was interested not in learning but in teaching, and although Calvin broke off the correspondence, Servetus sought to continue it by sending him not only a long series of letters but such various works of Calvin as he could obtain, to which he added insulting marginalia. It was foolhardy and useless except for the enmity that it aroused in Calvin.—Charles D. O'Malley. *The Complementary Careers of Michael Servetus: Theologian and Physician.* History of Medicine and Allied Sciences **8**: 386, 1953.

# CLINICAL PROGRESS

## A Consideration of Hemodynamic Criteria for Operability in Mitral Stenosis and in Mitral Insufficiency

*By* RÉJANE M. HARVEY, M.D., AND M. IRENÉ FERRER, M.D.

TEN years have elapsed since stenosis of the mitral valve was shown to be a surgically remediable lesion by Bailey[1] and Harken and associates.[2] Because effective surgery is now the province of a number of clinics, a great deal has been learned about rheumatic heart disease in its varied aspects and today there should be an unassailable hemodynamic formula or formulae for the selection of the patient for operation. Unfortunately there is still no simple answer.

The most direct approach to the assessment of a significantly stenotic mitral valve would appear to lie in the measurement of the diastolic pressure gradient across the mitral valve. Catheterization of the left heart using the method of Facquet and associates,[3] Allison and Linden,[4] or Bjorck and co-workers[5] has rendered this feasible. It has been shown from this type of study and from those made in the operating room that a diastolic gradient does exist across a stenotic valve and that this gradient will diminish or disappear following successful surgery. It might therefore be expected that determination of the gradient would indicate which lesion demands commissurotomy.

However, the diastolic pressure gradient across the mitral valve is a reflection of at least 3 variables: the degree of stenosis, the blood flow across this valve, and the time during which this flow passes the valve. It has only been in the last 18 months that the diastolic gradient, blood flow, and heart rate have been simultaneously measured in a few clinics and since the ultimate results of surgery in this modest number of patients[6, 7] has as yet not been ascertained, we are still in ignorance of what constitutes a significant gradient and of what conditions must be fulfilled.

A considerable body of data has been secured by right heart catheterization, although this information is less direct. Utilizing this technic and measuring heart rate, blood flow, and pressure, we have learned which hemodynamic alterations are found in patients with mitral stenosis and which of these variables will be returned toward normal by successful surgery.

### MITRAL STENOSIS

This part of our discussion is limited to the findings in patients with isolated mitral stenosis. Therefore subjects with enlarged left ventricles, mitral regurgitation, or significant aortic or tricuspid lesions are specifically excluded.

There are at present 6 hemodynamic patterns that can be found in patients with the auscultatory findings of mitral stenosis. The individuality of each pattern becomes apparent when viewed in relation to the entire clinical picture.

The expected and most universally accepted picture of an obstruction at the mitral valve is one originally described by Dexter and associates[8] in which at rest there is moderate to severe pulmonary hypertension, and elevation of the pulmonary wedge pressure, and a cardiac output that is slightly or moderately

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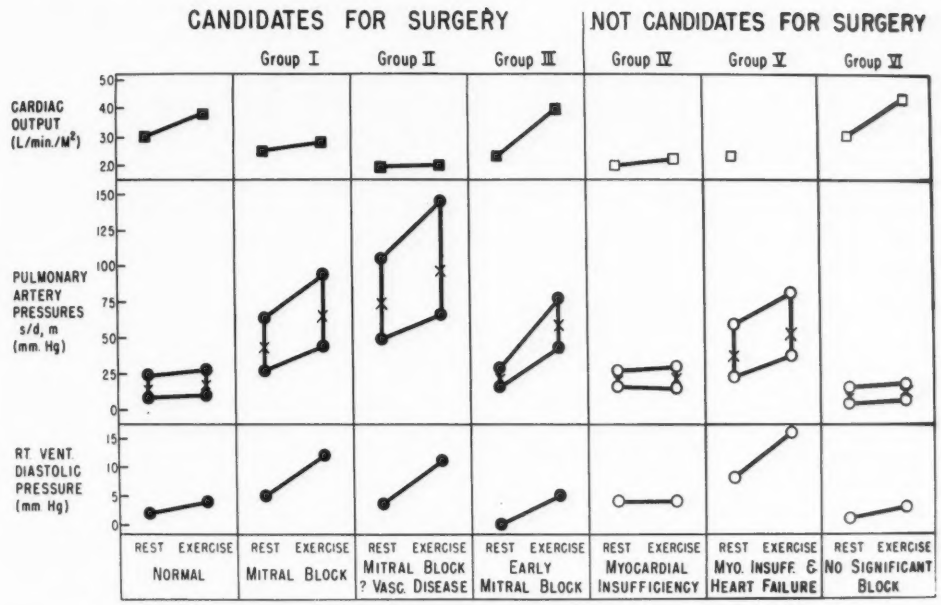



FIG. 1. Hemodynamic data at rest and during supine leg exercise in 6 groups of patients with mitral stenosis. Each group is represented by an actual study of an individual patient.

reduced (fig. 1, group I). These findings occur at heart rates that fall within the accepted normal range of 60 to 100 beats per minute.

In this group of patients the diastolic pressure in the pulmonary artery usually lies between 20 and 30 mm. Hg, the systolic pressure between 40 and 75 mm. Hg, and the mean between 30 and 50 mm. Hg. The pulmonary artery pulse pressure is strikingly increased. The mean pulmonary wedge pressure is quantitatively the same as the pulmonary artery diastolic pressure.

The inference from these data is that significant or severe obstruction to left atrial outflow has occurred at the mitral valve and that there is a consequent increase in the volume of blood in the left atrium. This in turn causes a rise in pressure in this chamber that is reflected in the elevated pulmonary artery diastolic pressure. In these individuals diastolic run-off from the pulmonary arterial tree is influenced chiefly by the obstruction of the mitral valve. The pulmonary artery systolic and pulse pressures rise more strikingly than the diastolic because they are influenced not only by the elevation of the left atrial pressure but also by the distensibility characteristics of the vessels themselves, i.e., the caliber and elasticity of the vessels, the volume of blood in them, and pulsatile flow.[9] In reviewing the available data one is struck by the tremendous variation in the level of cardiac output which is recorded in this type of patient; markedly reduced as well as normal values have been found. Even if one takes into consideration that all patients were not studied in the basal state nor were all free of apprehension or medications, nevertheless, in individual series a wide range of blood flow is apparent. It is known that atrial arrhythmias, fibrillation or flutter, can reduce cardiac output, but even in their absence low levels of blood flow are found. Attempts at correlation with pulmonary artery pressures or wedge pressures yield no consistent results. Correlations with such calculations as "pulmonary vascular resistance" and "mitral orifice size" prove little as the level of blood flow is an in-

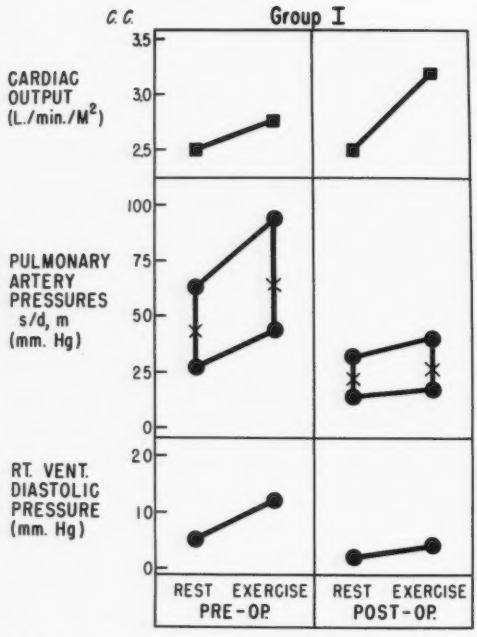



FIG. 2. Comparison of hemodynamic data at rest and during exercise in a patient (C.C.) from group I before and after mitral commissurotomy.

tegral part of these calculations. If the size of the mitral orifice is not the sole determinant of cardiac output, what other modality is? It is suggested that the integrity of the ventricular pump may well play a role.

The majority of patients who demonstrate this pattern should have a successful result from mitral surgery, and indeed they do (fig. 2). The mean wedge pressure and pulmonary artery diastolic pressure return toward normal. The pulmonary artery systolic and pulse pressures fall even more strikingly, thereby supporting the importance of the state of overdistention of the pulmonary arterial tree prior to surgery. The cardiac output does not, however, show the same striking change. In most series, the resting level of blood flow is much the same as preoperatively, although it may rise during exertion, when preoperatively it remained fixed. It appears to us that the best explanation for this lack of change in output, despite a marked fall in pressure, lies in the fact that existing myocardial damage has not been reversed by surgery and that mitral block is not the sole regulating factor in determining the level of cardiac output.

Another hemodynamic pattern that may be encountered is similar to the one previously described except in the magnitude of pulmonary hypertension, which is much greater and may be formidable in this second group (fig. 1, group II). The pulmonary wedge pressure is not much greater and indeed may lie within the same range as in the first group. Pedersen,[10] who has studied this pressure in many types of heart disease, has commented on the fact that one rarely encounters a wedge pressure of over 40 mm. Hg under the usual conditions of study. A review of the literature so strongly supports this view that one can probably say that those which have been recorded above this level are probably the result of manifest pulmonary edema as previously suggested by Gorlin and associates[11] or reflect a technical error. What factor is responsible for the finding that the pulmonary hypertension is much more severe in this second group although the wedge pressure is not, if any, higher than in the first group? It may well be a consequence of anatomic changes in the walls of the pulmonary vascular tree. In support of this argument one may cite the fact that in this group one rarely sees an almost normal resting level of pulmonary arterial pressure following commissurotomy even when the wedge pressure has fallen satisfactorily. Furthermore, serial observations in the same patient over a period of months may show a progressive fall in pulmonary artery pressures, which most reasonably is ascribed to progressive change in the pathologic lesions of the arterial tree. Indeed, one may see striking changes in pressure and in the electrocardiogram over a prolonged period of time (fig. 3). Similar serial changes have not been noted in heart size as seen by the x-ray.

Perhaps, too, the high pulmonary artery pressures are an indication that the limits of distensibility of the system have been reached.

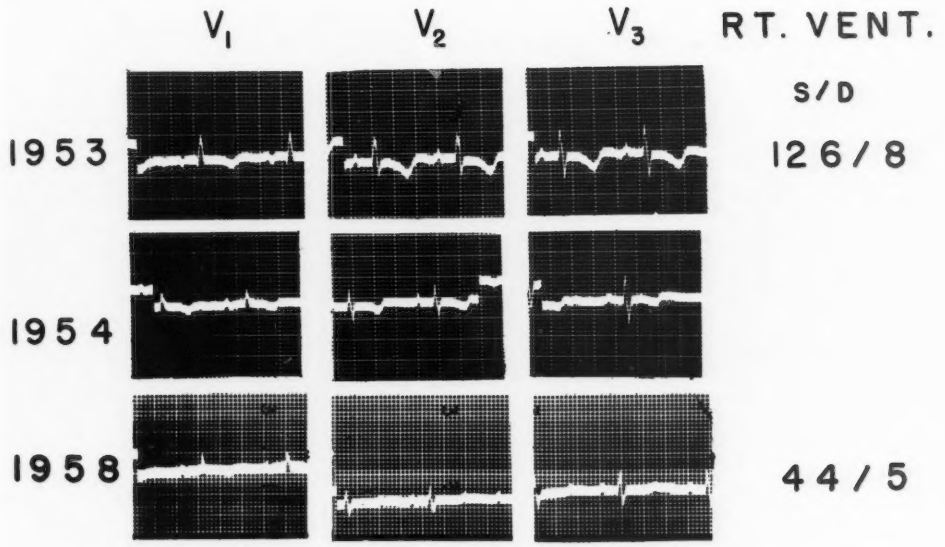



FIG. 3. The right precordial V leads and right ventricular systolic and diastolic pressures in a patient from group II before (1953) and after (1954, 1958) mitral commissurotomy.

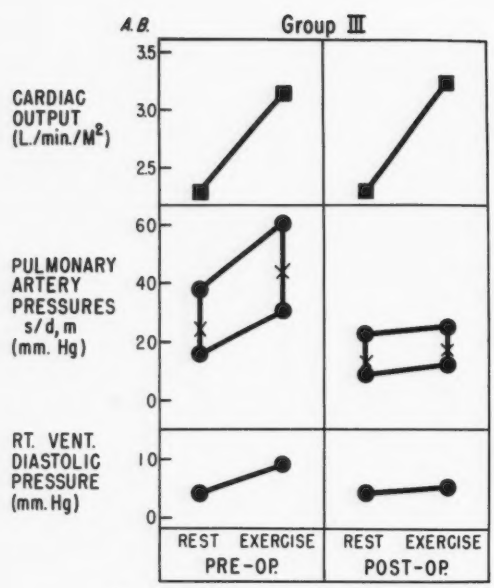
This conclusion is based on the observation that the pulmonary artery pressures, particularly the pulse pressure, do fall early and strikingly following surgery even if they do not return to the same level as in the previous group; hence, all this hypertension is not solely on the basis of pathologic anatomy.

There is evidence then for at least 2 factors that are responsible for the striking rise in pulmonary artery pressures in this second group: one, the pathologic changes in the vascular tree, which may be in part reversible after surgery; and the other, overdistention of the vascular system, which responds immediately to successful opening of a stenosed valve.

The third and fourth groups to be described may resemble each other hemodynamically at rest, but clinically, particularly historically, they may be distinguishable.

The first of these represents mild but significant mitral block (fig. 1, group III). The patients often complain of dyspnea only when under more than usual duress. Cardiac size is slightly increased and the electrocardiogram is within normal limits. Catheterization studies reveal either normal pressures or only minor elevations in pulmonary artery and wedge pressures at rest. The cardiac output may be normal or strikingly reduced. On exercise blood flow is increased normally, but the pulmonary artery pressures rise briskly, achieving levels not unlike those encountered in the first group at rest. Certainly the valve orifice is not so small as encountered in the previous 2 groups, but under conditions of stress, as in exercise or pregnancy, when there may be an increase in heart rate, cardiac output or blood volume, the stenosis becomes important. Surgery in these individuals with a mild but significant degree of stenosis results in a normal level of pressure on exercise (fig. 4). The resting level of blood flow may not be materially affected.

The fourth group (fig. 1, group IV) is hemodynamically not dissimilar from the third at rest—yet, clinically there is little doubt that we are dealing with another entity. In these individuals disability is as great as is encountered in those with moderate or severe resting hypertension. Indeed a story of repeated bouts of congestive failure is often



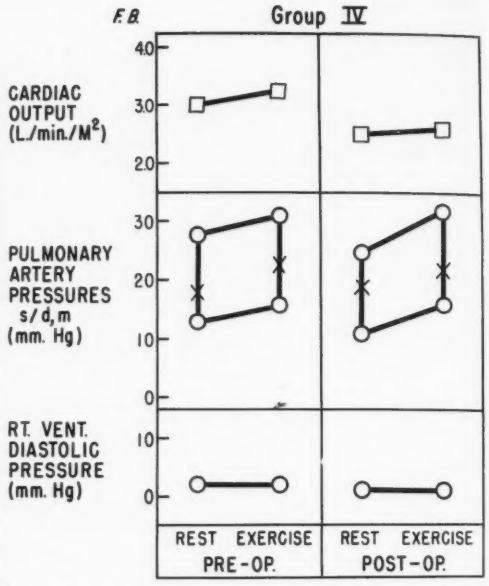




FIG. 4 *Left.* Comparison of hemodynamic data at rest and during exercise in a patient (A.B.) from group III before and after mitral commissurotomy.

FIG. 5 *Right.* Comparison of hemodynamic data at rest and during exercise in a patient (F.B.) from group IV before and after mitral commissurotomy.

elicited. The heart size is large, sometimes even larger than those with far greater pressures, and atrial fibrillation is often present. Although this group does not differ at rest from those with early mitral block, their hemodynamic response to exercise is not the same. In these individuals blood flow does not increase normally and the pulmonary artery pressures either do not rise, or do so modestly. Surgery does not change either the clinical course or the hemodynamic picture (fig. 5). It is easy to incriminate the surgeon for the lack of success but it is more likely that myocardial insufficiency is the responsible agent for both the hemodynamic and clinical picture and that valvular stenosis is not the predominant lesion.[12, 13]

This fourth group is the most frequently confused clinically with those who have tight mitral stenosis because of the degree of their disability, but hemodynamically they can be separated. However, when these patients with myocardial insufficiency are in congestive failure (fig. 1, group V) pulmonary hypertension and an elevation of right ventricular diastolic pressure develop. Hence their resting pulmonary hypertension might lead one to suspect mitral block rather than advanced myocardial insufficiency. The true state of this fifth group can be clarified by the finding of an elevated right ventricular end-diastolic pressure and by the rigorous use of all medical therapies. If such patients are studied following the relief of congestive heart failure, marked falls in the lesser circuit pressures will be noted. In the absence of such studies or in the presence of chronic irreversible failure, the nature of the hypertension cannot be elucidated and such patients should be considered for surgery with caution, if at all. In our experience surgery has not altered the clinical or the hemodynamic picture (fig. 6).

Finally, in patients who display normal cardiodynamics at rest and during exercise (fig. 1, group VI) there is no indication for surgery as has been shown by Claps et al.[1]

### Mitral Insufficiency

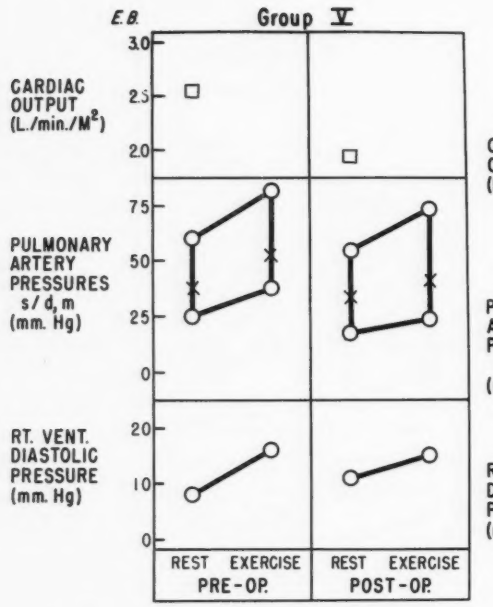
While successful surgery in mitral stenosis has permitted a definition of the hemodynamic consequences of this lesion, to date, with few exceptions, mitral regurgitation has not proved amenable to operation. Hence, one is secure in stating which patient with mitral insufficiency should be offered surgery. This, however, is not the only problem. We do not know what, if any, hemodynamic abnormalities may be properly attributed to mitral regurgitation and are also at a loss as to how to identify a significant lesion.

In 1922 Wiggers and Feil[14] published a detailed analysis of the hemodynamic effects of experimentally produced mitral insufficiency. Among some of their conclusions are the following: 1. Mitral regurgitant flow occurs chiefly in the latter part of ventricular systole and in very early diastole causing a rise of pressure in the left atrium in this interval. With the opening of the mitral valve, the regurgitant volume passes into the left ventricle, so that during diastole, left atrial pressure is not increased. 2. Left ventricular diastolic volume and pressure are increased as a consequence of the return of the regurgitant volume. 3. The rise in ventricular filling pressure, by producing a greater systolic discharge, serves to maintain aortic flow at an almost normal level. They further inferred that right ventricular output is unaltered and found that pulmonary artery systolic and diastolic pressures were not elevated by the production of mitral insufficiency and conclude that "as long as cardiac muscle is efficient, the increased volume of blood contained in the left auricle during systolic ejection is accompanied by expansion of the left auricle and its venous tributaries. Consequently no 'back pressure' effects are produced in the pulmonary artery or right heart." Lesser circuit hypertension could be produced, however, if arterial resistance was increased in the systemic circulation as then regurgitation would be greater than could be accommodated in the left veno-atrial system. Braunwald, Welch, and Sarnoff[15] have recently extended the observations in experimentally induced mitral insufficiency and have shown that the effect of any given regurgitant volume on left atrial pressure is a function of the filling pressure of the left ventricle.

Applying these considerations to man one could then predict that isolated valvular mitral regurgitation would cause no change in lesser circuit pressures, an elevation of left atrial pressure in late systole and very early diastole without much change in mean left atrial pressure, a minor increase in left ventricular end-diastolic pressure if the ventricle is not otherwise embarrassed, and a normal level of pulmonary and systemic blood flow.

The characteristic left atrial pressure curve of mitral insufficiency has been recorded on numerous occasions in man. Although recently, as would be predicted from experimental studies, normal levels of blood flow and lesser circuit pressures have been noted in man in the presence of isolated mitral insufficiency (fig. 7), these individuals were almost entirely asymptomatic.[16] In contrast to the experimental animal and the asymptomatic subject, the symptomatic patient said to have isolated or predominant mitral insufficiency is usually found to have pulmonary hypertension, left atrial hypertension, and a reduced cardiac output. Measurements of left ventricular diastolic pressure are few but both normal and elevated levels have been recorded.[17, 18]

Quite a few explanations can be offered to reconcile the differences between the experimental and clinical observations. The experimental studies are acute and little is known of the chronic effects of mitral insufficiency. It is possible that ultimately left ventricular function may be disturbed by the continuing effects of a large diastolic inflow and that left ventricular failure ensues with a consequent rise in filling pressure and a further increase in regurgitant flow that cannot be contained solely by the left veno-atrial system. This train of events, as recently postulated by Edwards and Burchell,[19] places the primary defect in the insufficient valve. It is also con-



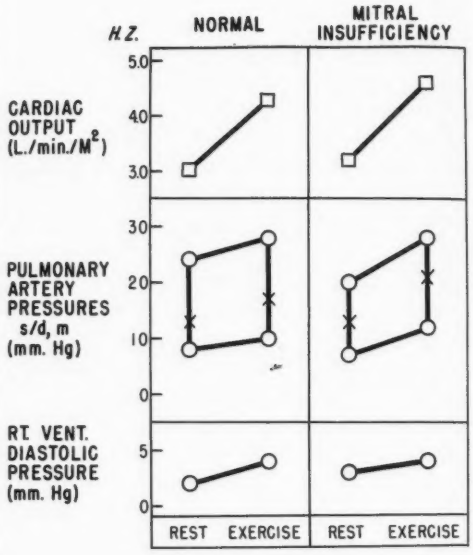




FIG. 6 *Left.* Comparison of hemodynamic data at rest and during exercise in a patient (E.B.) from group V before and after mitral commissurotomy.

FIG. 7 *Right.* Hemodynamic data at rest and during exercise in a patient (H.Z.) with pure mitral insufficiency. (From the work of Claps, Kaltman, Harvey, and Kossmann.[13])

ceivable that damage to the myocardium independent of the valve lesion is responsible for the aggravation of an otherwise innocent valvular lesion. This idea is strengthened by recent reports of open heart surgery on patients with mitral insufficiency[20, 21] in a number of whom marked dilatation of the annulus was found with virtually normal valve leaflets. The mechanism by which annular dilatation occurs must therefore be considered separately. If one invokes left ventricular myocardial failure secondary to rheumatic myocarditis or aortic valvular lesions, then one can account for the elevated left ventricular diastolic and lesser circulation pressures as well as the reduced cardiac output. Experimental studies on chronic mitral insufficiency, as recently begun by Kuykendall et al.[22] may eventually reveal whether the hemodynamics associated with mitral valvular insufficiency can in truth produce left ventricular failure and hence elevation of lesser circulation pressures and reduced output, or whether it is not myocardial failure that produces annular dilatation and aggravates an otherwise innocent valvular lesion.

A second explanation would stress that in the experimental preparation valvular incompetence is not so great as is encountered in man. There is no way to support or deny this at present.

Dexter and associates[17] have recently offered a third possibility. In studies in man they, as have Marshall et al.,[23] found that a diastolic pressure gradient exists between the left atrium and left ventricle. This phenomenon has not been noted in animal experiments. The implication is that in man mitral regurgitation rarely exists in the absence of mitral stenosis. During diastole a large flow must cross a valve orifice that is not normal, albeit not markedly stenosed; this results in an in

crease in left atrial volume and pressure which is reflected in the pulmonary vascular tree.

At present, then, it cannot be stated with certainty which hemodynamic abnormalities may be ascribed to mitral valve insufficiency, which laid to resulting or concomitant ventricular damage, or which reflect associated valve lesions.

Currently efforts are being directed at the documentation of the presence of mitral insufficiency and an estimation of its severity. Both the pulmonary wedge tracings and left atrial curves reflect the characteristic contour associated with this lesion. However, the same contour is seen if atrial fibrillation is present and little mitral regurgitation exists. Furthermore detailed analysis of these curves, including the height of the regurgitant wave, its slope, etc., do not permit a clear-cut definition between mild and severe degrees of regurgitation. Calculation of "mitral orifice size," particularly if insufficiency is suspected, requires measurement of the left atrial and left ventricular pressure levels and of both forward and regurgitant flow.[17] Pressure levels and forward flow can be secured, but an estimation of regurgitant flow eludes us. Following the lead of Korner and Shillingford[24] several clinics are now attempting this, but at present, theoretical as well as practical objections must be overcome before one can accept such data without question.

In conclusion, since the hemodynamic alterations produced by mitral insufficiency in man are not well defined and the hemodynamic assessment of the degree of the regurgitation is not yet possible, hemodynamic indications for repair of this lesion cannot be stated at present.

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## FINDING AND SEEKING

Arthur Stanley Eddington

English astronomer, 1882-1944

It is with thoughts of the relation of man to the visible universe that the scientifically minded among us approach the problem of his relation to the unseen world. Scientific theories have blundered in the past; they blunder no doubt to-day; yet we cannot doubt that along with the error there come gleams of a truth for which the human mind is impelled to strive. We seek the truth; but if some voice told us that a few years more would see the end of our journey, that the clouds of uncertainty would be dispersed, and that we should perceive the whole truth about the physical universe, the tidings would be by no means joyful. In science as in religion the truth shines ahead as a beacon showing us the path; we do not ask to attain it; it is better far that we be permitted to seek.—*Science and Unseen World.* From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. II, Boston, The Beacon Press, 1953.

# CLINICAL CONFERENCE

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## Atrial Tachycardia, Flutter, and Fibrillation

*By* R. H. LYONS, M.D., A. FARAH, M.D., G. K. MOE, M.D., PH.D., AND J. A. ABILDSKOV, M.D.

DR. RICHARD H. LYONS: Today we are going to discuss abnormal atrial rhythms. It has always seemed strange to me that though the physiologists have described delirium cordis since the beginning of vivisection, abnormal atrial rhythms were not recognized clinically until approximately 1880, when Sir James Mackenzie was able to notice in pulse tracings that the atrial impulse of the venous pulse disappeared in some patients who had irregular heart beats. Fast heart rates had been noticed earlier and William Stokes had described in 1856 a typical example of paroxysmal atrial tachycardia in a patient who was relieved by emetics. It was not until 1906, however, that Cushny and Edmonds were able to relate the phenomenon of atrial fibrillation in man to atrial fibrillation in animals. In 1908 Rothberger of Vienna proposed the theory that atrial dysrhythmias arose from multiple ectopic foci, and in 1920 Sir Thomas Lewis proposed the theory of a circus rhythm. In spite of these conflicting theories, little attention was paid them until recently when a variation of the Rothberger concept was revived as the sole cause of abnormal atrial activity.

Because of time we will not discuss atrial extrasystoles per se except to mention that they may have many potential causes but only occasionally can cause and effect be clearly demonstrated in man. Our discussion will involve primarily three types of abnormal atrial activity: atrial flutter, atrial fibrillation, and paroxysmal atrial tachycardia. Dr. Farah, how do you resolve the conflict between an ectopic focus and a circus rhythm as the cause of these abnormal rhythms?

DR. ALFRED FARAH: In recent years a unitary theory of production of atrial arrhythmias has been proposed that attempts to explain all the atrial arrhythmias on the basis of a rapidly firing ectopic focus. This hypothesis has its main merit in being a relatively simple and easily understandable concept. However, this simplified hypothesis cannot stand up to the experimental test. It has been shown by Rosenblueth and Garcia Ramos that in dogs one can set up a self-perpetuating type of atrial flutter that conforms to a circus movement. The important factors that determine a circus movement are the length of the pathway surrounding an obstacle, the conduction velocity of the impulse, and the refractory period of the tissue. The longer the pathway surrounding an obstacle the more likely it is to produce a circus movement. Everything else being equal, a short pathway will prevent the setting up of a circus movement. Refractory period determines the rate as well as the persistence of a circus movement. Prolongation of the refractory period will decrease the rate and finally will abruptly stop the circus movement. Conduction velocity is also an important factor, any increase in conduction velocity would tend to stop while a

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decrease in conduction velocity will tend to perpetuate the circus movement. It is also possible to produce atrial flutter by injecting a few micrograms of aconitine into the atrium. This type of flutter first described by Sherf, in its simplest form, behaves like an ectopic focus discharging regularly at rates of 400 to 600 beats per minute. The amount of aconitine injected influences the frequency of discharge from such foci. Thus, experimentally at least, one can produce 2 types of atrial flutter: one which conforms to a circus movement, the second conforming to the focal discharge hypothesis. It is not too difficult to demonstrate that both types of flutter can co-exist in the same atrium; thus a third type, namely, a mixed type of flutter can be demonstrated in the dog. There is no reason to believe that the basic types of flutter produced experimentally in the dog cannot also occur in the human heart.

The change of flutter to fibrillation and the change of fibrillation to flutter can also be demonstrated in the dog. Vagal stimulation, either directly or reflexly, readily converts a flutter of either type to atrial fibrillation.

DR. LYONS: Dr. Moe, I know you agree with Dr. Farah that it is unrealistic to believe that there is a single mechanism of atrial flutter —is this also true as an explanation of atrial fibrillation?

DR. GORDON K. MOE: According to either hypothesis it is believed that the regular electrical oscillations occurring either in the electrocardiogram or in direct recordings from the atrium are produced when the mechanism of origin has a sufficiently slow rate so that the atrium can be activated as a whole with each successive discharge of the ectopic pacemaker or each successive circuit of the circus movement. Fibrillation is diagnosed when the rate of discharge of an ectopic focus is so rapid that due to the refractoriness of part of the atrium regular excitation cannot occur, or when the circus movement about an obstacle occurs so rapidly that regular activation of the entire atrium cannot occur. The fundamental difficulty with both of these notions as an adequate description of atrial fibrillation is that it is hard to believe that either small circus movements or ectopic pacemakers could be endowed with the necessary stability to persist for many years as atrial fibrillation commonly does. It becomes necessary then to construct an explanation for atrial fibrillation that is consistent with the observed behavior, namely, the long persistence of fibrillation.

If one stimulates the atrium, an impulse will be transmitted uniformly and essentially concentrically to all extremities of the atrium and if the frequency of stimulation of the atrium or the frequency of initiation of impulses from whatever agency is sufficiently slow, orderly excitation of the atria will occur. If, however, an impulse is initiated at a time when recovery is incomplete and the atria are irregularly excitable, the propagation of such an impulse cannot be regular and disorganized atrial activity must be apparent in the electrocardiogram or in direct electrograms. When an impulse has been propagated through atrial muscle, it would be expected that the recovery wave should follow the excitation pathway with essentially the same concentric form. However, the duration of the refractory period in atrial muscle is not uniform. In various portions of the atrial muscle differences of as much as 40 msec. can be demonstrated in the ordinary preparation of an anesthetized dog with an open chest and much greater differences can be elicited by vagal stimulation. If the atria do not recover in the same sequence as the fibers have been activated, irregular propagation must occur whenever an early premature impulse is initiated in the atrium. If this premature impulse is propagated irregularly, it would be expected that it would move slowly through areas in which the muscle was partially refractory, since conduction velocity is depressed in partially refractory tissue. It would move more rapidly in those areas that had fully recovered, and it becomes apparent then that the wave front of this impulse should conform itself to the retreating edge of the previous excitation wave. In other words, this advancing wave front should be

co ıe serrated and irregular. If a second premature response is initiated at the same or at a different site immediately following the first premature response, it now falls in tissue that is even more irregularly excitable. It also follows that this advancing wave front must become more serrated and more irregular, with advancing tongues moving around islets of tissue so refractory that they escape excitation entirely. In other words, the wave front for the third or perhaps the fourth of a series of premature beats in the atrium might be expected to become fractionated. If we assume that fractionation of this sort can occur (and this assumption is common to most discussions of the mechanism of atrial fibrillation since the very earliest descriptions 50 or 60 years ago), it becomes apparent that orderly excitation of the atria is no longer possible. The wave front will have broken into isolated independent wavelets that can circulate at random. These wavelets would be changing in number, changing in conduction velocity, and changing in pathway constantly as the disorder persists. Two wavelets meeting about an island of refractory tissue would be expected to fuse and become one. On the other hand, a larger wavelet may split about an island of refractory tissue or a peninsula of such tissue and become divided into 2 independent wavelets.

It now becomes necessary to explain why fibrillation can persist as long as it does. It seems obvious that the greater the number of such independently circulating wavelets the less is the likelihood that these could fuse into a single wavelet which would terminate the dysrhythmia. If there are few such wavelets the statistical probability that they might fuse and fall into phase with all of the muscle becoming refractory or excitable at the same instant is relatively large. If on the other hand the number of wavelets is very large, the statistical probability that they would fall into phase and terminate the dysrhythmia becomes vanishingly small.

We shall now consider those features of atrial behavior that would determine how many of such randomly circulating wavelets could coexist. First in importance is, of course, the size of the atria. A large mass of atrial muscle can certainly support or contain a larger number of wavelets than a small mass of atrial tissue. Furthermore, if the refractory period is short, the total number of such wavelets should be large. If the refractory period is very long, for example, the whole atrium will remain refractory following an excitation process, and fibrillation would be impossible. Conduction velocity must also be an important factor. If conduction velocity were very rapid, any excitation process would be rapidly propagated to the most remote extremes of the atria; all of the fibers would be forced into phase; and the dysrhythmia could not continue. So we have these 3 factors which favor the maintenance of fibrillation, once induced: first, the mass of the atrial muscle; second, the duration of the refractory period; third, the conduction velocity.

DR. LYONS: Dr. Moe, you have expressed this concept of atrial fibrillation more clearly than I have heard it in the past. What kind of evidence exists to support this concept and how do you relate this to the hypothesis of focal discharge and circus rhythm?

DR. MOE: Garrey described one of the crucial experiments about 1914 when he showed that if he divided an isolated fibrillating heart into sufficiently small pieces fibrillation was arrested. It was implied by Garrey that when the mass of muscle had been reduced to a sufficiently small magnitude, circus movement of the kind he postulated was no longer possible because no pathway was long enough. It would also follow in terms of the present theory that when the mass has been reduced by cutting, the residual piece of tissue can no longer contain a sufficiently large number of wavelets to sustain fibrillation. When fibrillation is produced in a dog heart by rapid electrical excitation, this fibrillation will be self-sustained provided the vagus nerves are stimulated. Stimulation of the vagus, of course, reduces the mean refractory period of the atrial tissue and would therefore be expected to increase the total number of wavelets. Fibrillation so induced in the dog heart

is always self-limited within seconds after the initiating agency is turned off when the vagi are not stimulated, which implies that the total mass of tissue in the usual dog atrium is not large enough to sustain atrial fibrillation in the absence of some accessory agency. When atrial fibrillation is induced by rapid stimulation of the atrial appendage and is maintained by stimulation of the vagus nerve, clamping of the atrial appendage with a stout surgical hemostat immediately interrupts fibrillation in the appendage from which the dysrhythmia originated while fibrillation continues uninterrupted in the body of the atrium and will continue as long as vagal stimulation is continued.

Another piece of evidence in support of the notion that a large mass is required to support an adequate number of wavelets is a recent observation at the School of Veterinary Medicine at the University of Pennsylvania where fibrillation was produced in unanesthetized cattle weighing about 1,000 pounds each. Fibrillation was produced by intra-atrial stimulation with electrodes introduced through a jugular vein catheter. In these cattle fibrillation persisted for days or weeks in the absence of medication and in the absence of vagal stimulation. In fact, fibrillation was not abolished in these animals by the administration of doses of atropine up to 1 mg. per Kg. Under these circumstances one may conclude that the atria of animals of this size are sufficiently large to support an adequate number of randomly wandering wavelets even in the absence of abbreviation of the refractory period through the agency of vagal stimulation.

DR. LYONS: Dr. Moe, from this description of atrial fibrillation one really wonders how atrial fibrillation ever spontaneously stops, which we know that it does clinically. Certainly your explanation also has many clinical analogies, such as the frequency of atrial fibrillation associated with mitral stenosis or mitral insufficiency where there is enlargement of the atria. Do you have any ideas why we do occasionally see atrial fibrillations spontaneously ceasing?

DR. MOE: No matter how many such independent wavelets might coexist in the atrium, there is nevertheless a statistical possibility that they may fall in phase and, therefore, the dysrhythmia may be self-limited. One might add that this conforms with the opinion of Dr. Frank Wilson, who often said that when fibrillation stopped it was an accident and that with drug therapy one merely set up the conditions to permit this accident to occur more readily.

DR. LYONS: Certainly the physician did not do it directly by administering drugs, but we do know that we can administer certain drugs such as quinidine that will be effective in setting up these conditions.

Dr. Farah, can you tell us about the actions of quinidine and digitalis as they relate to the concepts of flutter and fibrillation presented?

DR. FARAH: It is possible to explain some of the effects of some of the important drugs used in the treatment of these arrhythmias. The quinidine-like substances when studied on a circus-movement type of flutter reduce the atrial rate and usually proportionately increase the ventricular rate. Once atrial rate has been reduced to values around 300 to 350 beats per minute one suddenly sees a short period of electrical quiescence followed by a reversion to a sinus rhythm. This effect of quinidine can also be demonstrated in a focal discharge type of flutter and here the atrial rate has to be reduced to much lower values before reversion to a normal rhythm is seen. Furthermore, a circus type of flutter requires smaller amounts of quinidine for reversion than an aconitine (focal discharge) type of flutter. In atrial fibrillation quinidine and quinidine-like substances frequently first convert the fibrillation to a flutter followed by the reversion to a normal rhythm. The effects of quinidine on the electrical properties of cardiac muscle explain to some extent the slowing and reversion to a normal rhythm. The most significant point is the increase in the refractory period produced by quinidine and quinidine-like substances, which is dependent on dosage. The decrease in flutter

rate is due to a decrease in conduction velocity produced by quinidine. Thus, the increase in refractory period tends to stop while the decrease in conduction velocity tends to perpetuate the circus movement. The resultant of these 2 effects of quinidine is quite unpredictable and it is a question of chance or accident that the flutter suddenly reverts to a normal rhythm. With quinidine one can consistently stop a circus type of flutter in the dog provided one uses enough of the drug. This is not always the case with an aconitine (focal discharge type) induced flutter, where one occasionally has to use large amounts of quinidine, which produce severe ventricular disturbances and even ventricular fibrillation.

The effects of quinidine on a focal discharge are due to the ability of quinidine to suppress impulse production. This effect of quinidine can be demonstrated in both normal and abnormal pacemakers. The suppression of impulse production by quinidine is rather poorly understood and it may be related to the effects of quinidine on the rate of entry of sodium ions during activity. Wiedman has shown that local anesthetics and probably quinidine decrease the rate of rise of the action potential and this in turn may be related to the rate of entry of sodium ions. These effects of quinidine on membrane permeability may conceivably explain the reduction in rate of impulse production and the changes in refractory period and conduction velocity. The effects of quinidine on atrial fibrillation are a reduction in the number of recorded impulses at any one point in the atrium and occasionally a change of the fibrillation to flutter. As Dr. Moe has already stated, the changes in refractory period, conduction velocity, and excitability produced by quinidine will tend to reduce the number of wavelets and thus decrease the fibrillation rate. The reversion to a normal rhythm here is a question of chance. Drug administration sets up a state in which the statistical probabilities are more favorable for the simultaneous stoppage of the multiple wavelets.

Digitalis effects on atrial flutter are rather complex and depend on the direct effects of digitalis glycosides on atrial muscle and the indirect effects mediated via the reflex activation of the vagus.

The direct effects which are studied in the vagotomized atrium are increase in refractory period and a decrease in conduction velocity and excitability. These changes cause a decrease in atrial flutter rate and finally a reversion to a normal rhythm. On the other hand, application of digitalis to an innervated heart frequently changes a flutter to a fibrillation. This change is mediated via the vagus, since cutting the vagi abruptly changes the fibrillation to a normal rhythm. The administration of atropine will do the same thing as cutting the vagi. One explanation for these findings is that the direct effects of digitalis, which tend to stop the flutter, are masked by the vagally mediated effects, which cause the fibrillation. If vagal effects are suddenly removed by atropine or vagal cutting, the direct effects come to the fore and tend to slow and finally to convert the flutter to a normal rhythm.

DR. LYONS: If this is true, and I have no doubt concerning your facts, then the clinician dealing with a patient with a sudden onset of flutter or fibrillation may make the conditions less likely for spontaneous conversion to normal if he uses digitalis. On the other hand, if he does not slow the ventricular rate, he may lose the patient. This clinical dilemma is usually easily resolved in favor of the patient, and digitalis is administered rather than atropine to control the ventricular rate. Quinidine is then used in an attempt to reset the stage for conversion. Certainly the administration of atropine or quinidine without previous digitalization may expose the patient to serious increases in ventricular rate. Can you resolve this dilemma for us, Dr. Farah?

DR. FARAH: No.

DR. LYONS: One type of atrial activity that is often favorably modified by increased vagal stimuli is paroxysmal atrial tachycardia. How does this differ from atrial flutter and atrial fibrillation, Dr. Abildskov?

DR. J. A. ABILDSKOV: I will consider paroxysmal atrial and atrioventricular nodal tachycardias together, since they have several characteristics in common. One point that needs emphasis is that these are clinical rather than experimental entities. As Dr. Farah and Dr. Moe have said, atrial fibrillation and flutter can be produced experimentally by a variety of means. In experimental animals these arrhythmias show most of the features of their counterparts in patients. Unlike fibrillation and flutter a disturbance with the characteristics of paroxysmal tachycardia cannot be regularly and reproducibly initiated in experimental animals. Repetitive stimulation electrically or chemically at rates comparable to those of paroxysmal tachycardia does not constitute the experimental counterpart of paroxysmal tachycardia, since it does not provide the opportunity to test vagal effects on the pacemaker. Since experimental paroxysmal tachycardia cannot be initiated at will, we actually have less precise knowledge of its nature than we do that of flutter and fibrillation.

In the absence of all but a few relevant experimental observations, the clinical characteristics are the major basis on which to postulate a basic mechanism. There are 3 such characteristics that seem to me most pertinent to the probable basic nature of these tachycardias. One is the occurrence of frequent supraventricular premature beats before or after the bout of tachycardia. This has been frequently observed and has been widely interpreted to indicate a similarity in the basic mechanism of premature beats and paroxysmal tachycardia. Since it is a widely held view that premature beats represent impulse formation in ectopic sites, it has been an easy step to view paroxysmal tachycardia also as rapid, regular impulse formation in an ectopic center. The point which now requires emphasis is that not all premature beats necessarily represent ectopic focal discharges. Experiments carried out by Dr. Moe and coworkers show that some premature beats actually represent a reciprocal rhythm in which an impulse originating in the atria is transmitted to the ventricles and also back to th atria. This second atrial response to a singl stimulus has been termed an "echo." At thi time it is not known whether the prematur beats exhibited by patients subject to paro ysms of tachycardia are ectopic focal di charges or "echoes" such as those produce in Dr. Moe's experiments. If they should b shown to be the latter, their occurrence woul actually constitute strong evidence agains the view that paroxysmal tachycardia consist of rapid impulse formation in an ectopi center.

A second feature of paroxysmal supraven tricular tachycardias that must be taken int account is a consideration of their basic natur in the absolute regularity of the cardia rhythm. This characteristic is extremely use ful diagnostically and is striking from the standpoint of physiology when it is considered that periodic fluctuations of autonomic tone do not influence the cardiac rate. This is a feature of paroxysmal tachycardia that is extremely difficult to attribute to ectopic focal discharge. The sinoatrial node, which is a site of impulse formation whose properties are reasonably well known, is certainly subject to variation in sympathetic and parasympathetic tone; it responds by altering the rate of impulse formation. While it is true that nerve fibers are more abundant in the sinoatrial node than in other portions of the atria, it would still seem that at least some atrial foci and atrioventricular nodal foci should be so located that variations in nervous tone would result in irregularity of impulse formation. That such irregularity is not a feature of paroxysmal tachycardia does not disprove the ectopic focus theory but does stimulate the search for another mechanism which would seem more likely to result in a regular cardiac rhythm.

A third characteristic of supraventricular tachycardia, which is both interesting physiologically and useful therapeutically, is th response to vagal stimulation. It is well know that such stimulation may have no effect bu that when it is effective, the result is abrup termination of the tachycardia. In those in

st nces where vagal stimulation has no effect o paroxysmal tachycardia, an ectopic focal m chanism is certainly possible. It has been d nonstrated that vagal fibers are not uni- f mly distributed in the atria and an indi- v lual focus might well be in an area not s ject to a sufficiently high concentration of a tylcholine to alter its performance. It is n re difficult to account on the basis of ectopic f al discharge for those tachycardias which a e terminated by vagal stimulation. As men- ti ned previously, the effect of vagal stimu- la ion on the normal cardiac pacemaker is to s w gradually the rate of impulse formation. I know of no reason to believe an ectopic fo- cus subject to vagal influence ought not to operate in a similar fashion with gradual slowing rather than abrupt cessation of pace- maker activity. We have then a second char- acteristic of paroxysmal supraventricular tachycardia which, while not disproving ec- topic focal activity, is difficult to account for on that basis.

The absolute regularity and the response to vagal stimulation of paroxysmal supraven- tricular tachycardia have led some to postu- late a mechanism other than ectopic focal activity. Doctors Barker, Wilson, and John- ston and Dr. Ashman considered these fea- tures to be more adequately explained on the basis of circus movement mechanisms. A re- circulating wave into and out of the sinus node was postulated for those tachycardias we label atrial in origin and a similar reentry into and out of the atrioventricular node for n dal tachycardia. Such a mechanism accounts n ely for the abrupt termination of paroxys- m l tachycardia on vagal stimulation, since t e alteration in refractory period so pro- d ced might suddenly block the reentry path. A reentry phenomenon also accounts for the r gular cardiac rhythm, since the excitation p th is fixed.

It must be apparent that in my opinion a r ntry phenomenon is the probable mecha- n m of paroxysmal tachycardia. The likeli- h d of such a mechanism has recently been e anced by evidence of a dual transmission s tem in the atrioventricular node and by experimental findings in 2 animals in which a dysrhythmia with the features of paroxys- mal tachycardia happened to occur. I wonder if Dr. Moe will discuss these findings and their relation to clinical paroxysmal tachy- cardia.

DR. MOE: Many of the postulated explana- tions for reciprocal rhythm and for paroxys- mal tachycardia have implied the existence of a dual transmission system due either to nonuniform alteration of the properties of the bundle of His, or of the node itself, or per- haps due to the existence of 2 discrete path- ways. Experiments which were carried out in our laboratories some 3 to 4 years ago elicited 3 features of atrioventricular transmission which are consistent with the existence of 2 normal pathways in all of the mammalian species that were examined. These features of atrioventricular transmission are, first of all, an unexpected excess temporal delay in the propagation of very early premature atrial stimuli to the ventricles; second, the frequent demonstration of atrial echoes following atrial premature excitation or ventricular echoes following premature ventricular excitation. This latter observation has recently been con- firmed by Rosenbleuth. It has been possible to produce atrial or ventricular echoes and even multiple echoes. Finally, there were con- figurational changes in the ventricular elec- trical response following very early prema- ture atrial excitation.

As Dr. Abildskov suggested, it is usually impossible to set up a true paroxysmal tachy- cardia experimentally. In fact, on only 2 or 3 occasions in more than 100 experiments on dog hearts we have observed spontaneous bouts of self-sustained tachycardia that have all of the features of the paroxysmal supra- ventricular tachycardia observed clinically, namely, the fixed cycle length, the onset fol- lowing immediately upon a premature atrial systole, and cessation upon the introduction either of premature beats in atrium, or ven- tricle or upon intense vagal stimulation.

DR. LYONS: Did you think that in these instances the dual transmission mechanism

from the atrium to the ventricle was involved?

DR. MOE: This was certainly our interpretation. The notion would be that the premature impulse finds 1 of the 2 alternate pathways in the transmission system excitable while the other is still refractory, makes its first trip to the ventricle over only 1 of the 2 pathways and by the time it reaches there finds the alternate pathway available and excitable for a return trip to the atrium.

DR. LYONS: Dr. Moe, would you summarize the points that have been covered in this conference?

DR. MOE: We know on the basis of experimental evidence it is possible to produce rapid atrial activity by means of a circus movement about one of the naturally occurring or an artificially induced obstacle in the atrial muscle. It is probable that the same phenomenon occurs spontaneously. It is also possible to produce rapid atrial activity by means of a rapidly discharging ectopic focus produced either by repetitive electrical stimulation or by the administration of aconitine. Since an ectopic focus can be produced experimentall , it seems reasonable to suppose that natu e occasionally performs the same experimer . It is therefore unnecessary, and indeed ev n unrealistic, to propose that only 1 mechanis n can exist to explain all of the atrial tach - cardias. It would be my conviction that c - tain instances of atrial tachycardia, wheth r regular or irregular, can be due to circ s movement activity. It is possible that so e instances of atrial tachycardia are due to e - topic focal activity and it is possible, and I believe probable, that self-sustained fibrill - tion however induced, whether by an ectop c focus or by a circus movement, is maintain d by the existence of numerous randomly ci - culating wavelets. It has been possible to pr - duce paroxysmal tachycardia in a few isolate d instances by means of premature atrial ex- citation under conditions that would fav r the exposure of the dual transmission system, and it is possible that the same situation oc- casionally occurs in atrioventricular nodal tachycardia in the human subject.

# ABSTRACTS

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## ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

**Malamos, B., Moulopoulos, S. D., Dimakis, D., and Sarkas, A.: Animal Experiments on the Electrocardiogram in Acute Cor Pulmonale.** Ztschr. Kreislaufforsch. **48:** 121 (Feb.), 1959.

In 20 dogs the intravenous injection of lycopodium seeds or constriction of the pulmonary artery caused inconstant changes in the P-R interval, slight prolongation of the Q-T interval, increase in the R wave, decrease in the S wave and sometimes the appearance of an R wave in the right endocardial leads. The T wave became more positive in right ventricular epicardial leads and usually more negative in left epicardial leads. The S-T segment showed elevation in right ventricular endocardial and epicardial leads, no change in left endocardial leads, and often depression in left epicardial leads. Trans-septal leads usually showed no change in the S-T segment. It was concluded that acute cor pulmonale caused injury in the lateral wall of the right ventricle, but not in its septal wall, and that in many instances subendocardial injury in the lateral wall of the left ventricle appeared; this was attributed to decreased coronary flow as a result of increased coronary venous pressure.

LEPESCHKIN

**Walker, S. M.: Ventricular Coupling Induced by Anodal or Cathodal Polarization during Continuous Direct Currents in Dog Ventricle.** Am. J. Physiol. **196:** 209 (Jan.), 1959.

Ventricular ectopic beats coupled with preceding normal beats occurred during the delivery of direct current when the anode or cathode was on the ventricular epicardium of the dog. These ectopic beats were induced within the T wave or immediately thereafter during the application of threshold direct current when the anode was on the epicardium. When anodal current was begun in the S-T segment of a given cycle, an ectopic beat was induced within or near the T wave of the same cycle. When the cathode was on the epicardium, coupled ventricular ectopic beats were induced within the P-R interval during the application of threshold current. Under these conditions, marked slowing of sinus rate by vagal stimulation did not alter the interval of coupling between the ectopic beat and the preceding normal beat. Thus, it was shown that abnormal ventricular beat, falling within the P-R interval, was ectopic and independent of the atrial impulse.

KAYDEN

**Zao, Z. Z., Yen, M., and Herrman, G. R.: Relation between S-T Segment Elevation and Experimental Myocardial Oxygen Gradient.** Am. J. Physiol. **196:** 207 (Jan.), 1959.

Myocardial oxygen gradient was altered variously by means of gas mixture inhalation in acute coronary artery occlusion in the dog. This was correlated with the S-T segment elevation in electrocardiograms recorded in a bipolar subepicardial lead across the pink and cyanotic areas of the myocardium. The electrocardiograms revealed a positive relation between them, that is, the S-T segment increased in height with the increasing of the oxygen gradient and decreased in height with the decreasing of gradient.

KAYDEN

**Geissler, W., Porstmann, W., and Wolf, W.: Retrograde Catheterization of the Left Ventricle through the Common Carotid Artery in the Pre-Operative Diagnosis of Aortic Disease.** Ztschr. Kreislaufforsch. 47: 1068 (Dec.), 1958.

Catheterization through the exposed right common carotid artery was carried out in 17 patients, and the left ventricle was reached in all. Continuous pressure registration during retraction of the catheter enabled exact localization of the stenosis. Filling of the left ventricle with dye enabled good visualization of its outflow tract and the aortic valves, as well as recognition of mitral regurgitation. The only complication was hemiparesis in a patient with mitral stenosis. Ventricular arrhythmias caused by contact of the catheter with the left ventricular endocardium always could be terminated by withdrawing the catheter slightly.

LEPESCHKIN

**Legrand, R., Linquette, M., Desruelles, J., Bonte, G., Gerard, A., and Garon, J.: Visualization of the Left Ventricle by Means of Retrograde Catheterization from the Femoral Artery.** Arch. mal. coeur 51: 1037, (Nov.), 1958.

A polyethylene catheter containing a fine steel wire was introduced through a trocar into the femoral artery, and the trocar then withdrawn. In order to prevent the catheter from entering the left subclavian artery the patient inclined his neck to the left. After passage of the aortic valves an intracavitary electrocardiogram was registered through the wire, and the latter withdrawn to enable dye injection, registration of pressures or oxymetry. The method allowed exact recognition of aortic disease and mitral regurgitation. It had the advantage of simplicity and good tolerance, but should not be carried out in old persons or those with vascular fragility, renal involvement, myocardial or coronary failure or active endocarditis. It may not succeed in persons with tortuous iliac arteries or marked coiling of the aorta. It should be carried out only if a surgical correction is contemplated.

LEPESCHKIN

**Schuldt, H. H., and Hoffman, F.: Contributions to the Continuous Bloodless Registration of Arterial Blood Pressure in Man. I. A New Pressure Pulse Transducer.** Ztschr. Kreislaufforsch. 48: 101 (Feb.), 1959.

A square rubber bag was completely encased in a metal box with adjustable walls. This fitted tightly against the radial artery where it crossed the carpal bones, accompanied by a tendon. The pressure in the bag was registered by means of a strain gage. The arm was completely immob lized. This method minimized the loss of puls pressure caused by tissue elasticity, so that regi tered pressures average 85 per cent of tho measured according to Riva-Rocci on the san arm or by means of an intraarterial cannula the other arm. The configuration of the pul registered by the 2 methods was nearly identic The pressure on the skin over the radial arte was tolerated well up to 3 hours.

LEPESCHKIN

**Heidel, W.: Clinical and Electrocardiograph Findings in Incomplete Right Bundle Bran Block.** Ztschr. Kreislaufforsch. 48: 47 (Jan , 1959.

In 5.6 per cent of all electrocardiograms a la e R′ wave in leads $V_1$, $V_2$, or $V_3r$ with a wide S wave in leads I and $V_6$ was registered. Of the e 242 curves, the QRS duration exceeded 0. 2 second (complete block) in 42, was 0.10-0. 2 second (typical incomplete block) in 47, and less than 0.10 second (atypical incomplete block) in 153 patients. The percentage of men was 77, 68 and 73 in the 3 categories respectively. Patients with heart and circulatory disease were predominant in the first group, those with pulmonary disease in the second, and those without heart or lung disease in the third group. S-T displacement and A-V conduction disturbances were found practically only in the first 2 groups, while low voltage predominated in the third group. Patients under 30 years of age had a considerable predominance of "atypical incomplete block," while those over 50 years of age had definite predominance of "complete block." It was concluded that "complete block" was clinically most significant while "atypical incomplete block" was least significant.

LEPESCHKIN

**Herrmann, G. R., Park, H. M., and Hejtmancik, M. R.: Paroxysmal Ventricular Tachycardia: A Clinical and Electrocardiographic Study.** Am. Heart J. 57: 166 (Feb.), 1959.

An analysis of 84 episodes of paroxysmal ventricular tachycardia in 60 patients is presented. There were 46 intermittent episodes with runs of 4 or more ectopic ventricular contractions of less than 30 seconds' duration recorded electrocardiographically and 38 persistent episodes with a continuous run of longer duration. No significant differences between the persistent and intermittent types were found in regard to age, sex, and race. In 6 patients there was no apparent heart disease. In 71 per cent there was atherosclerotic coronary ischemic heart disease with or without hypertensive cardiovascular di-

ase and in 12 per cent rheumatic heart disease. Many of the patients, particularly those with persistent paroxysmal ventricular tachycardia, suffered acute myocardial infarction. Ten per cent of the patients showed definite evidence of digitalis intoxication and in another 17 per cent digitalis overdosage could not be excluded. The symptoms and signs in these patients could be arranged in 3 categories: (1) those of the underlying heart disease, such as acute myocardial infarction or congestive heart failure; (2) those due to precipitating factors, such as digitalis overdosage, and (3) those due to tachycardia itself. The therapeutic agents employed in this series were quinidine, procaine amide, and morphine, either individually or in various combinations. The prognosis of paroxysmal ventricular tachycardia was found to be influenced by many factors. The rhythm was especially serious when it complicated acute myocardial infarction. The prognosis in the intermittent type was somewhat better than in the persistent type. Five patients with persistent paroxysmal ventricular tachycardia died of the abnormal rhythm itself.

SAGALL

**Lozada, B., and Tempone, N. D.: Electrocardiography in Exercise.** Acta cardiol. 13: 464, 1958.

The electrocardiographic response to exercise (150 to 160 steps in place performed within a minute) was studied in 20 normal subjects and in 15 patients with angina. In both groups there was generally an acceleration of rate. The P waves and P-R intervals revealed little change but the T wave often became more prominent and caused a false S-T depression. The QRS interval tended to deviate to the right secondary to positional variations. Alterations of the S-T segment occurred in both groups and the distinction between normal and abnormal response had to be based on the degree of the deviation from the isoelectric line, on changes in its configuration, and particularly on the timing of these alterations. In none of the normal subjects was a modification of the S-T segment present 5 minutes after exercise. Elevation or lowering of the T-wave amplitude was common to both groups and not infrequently occurred without any other electrocardiographic alteration; however, in none of the normal subjects did a T-wave change persist after 5 minutes. The corrected Q-T interval varied in an irregular fashion: in the normal subjects there was a tendency to shortening during the tachycardia in contrast to the anginal group in which a significant prolongation of $Q\text{-}T_c$ occurred.

PICK

**Doliopoulos, Th., Christopoulos, D., and Skalkeas, G.: Postoperative Electrocardiographic Modifications. A study of 260 Operated Cases.** Cardiologia 34: 1, 1959.

Preoperative and postoperative (between fifth and tenth day) electrocardiograms were recorded in 260 patients undergoing a variety of operations. There were 98 men and 162 women ranging in age from 18 to 68. In 52 of the 238 patients with normal preoperative electrocardiograms, postoperative changes were found; 4 of the 22 patients with abnormal preoperative tracings showed additional electrocardiographic changes postoperatively. Two thirds of the patients with abnormal postoperative tracings were less than 50 years of age. The electrocardiographic abnormalities were, in order of frequency: subepicardial ischemia, extrasystoles, negative T waves in $V_2$, subendocardial lesions, left bundle-branch block, right bundle-branch block, atrial fibrillation, left ventricular strain, long Q-T intervals, and short Q-T intervals. The importance of a thorough preoperative cardiologic evaluation in conjunction with the preanesthetic examination is emphasized.

BRACHFELD

**Hubbard, T. F., Dunn, F. L., and Neis, D. D.: A Phonocardiographic Study of the Apical Diastolic Murmurs in Pure Mitral Insufficiency.** Am. Heart J. 57: 223 (Feb.), 1959.

Phonocardiographic and physiologic studies of the apical diastolic murmurs and sounds found in high-grade pure mitral insufficiency are reported. A short middiastolic murmur with its major components corresponding in time to the rapid-filling phase of ventricular diastole was found to be the most consistent and characteristic diastolic murmur in these patients. It was of maximal intensity at the apex, had dominant frequencies in the range of 75 to 150 cycles per second; and its intensity pattern corresponded to a small atrioventricular gradient developing during rapid ventricular filling. In 14 patients a third heart sound was found. It corresponded in timing to the trough of the ventricular pressure wave in early diastole and the peak of the rapid-filling wave of the apex cardiogram. In the presence of prolonged A-V conduction and sinus rhythm a fourth heart sound and presystolic murmur occurred with the development of an atrioventricular pressure gradient during atrial contraction. In 12 patients the high-frequency systolic murmur of mitral insufficiency persisted from 0.03 to 0.10 second after the major components of the aortic second sounds. The extension of this murmur with its decreasing intensity beyond the time of closure of the

semilunar valves to the onset of the rapid-filling murmur with mitral opening was coincident with the decreasing ventriculo-atrial gradient through isometric relaxation.

SAGALL

**Effert, S., Domaning, E., and Erkens, H.: Potentialities of Ultrasonic Echo Technic in Cardiac Diagnosis.** Cardiologia 34: 73, 1959.

The ultrasonic echo technic permits continuous recording of the motion of certain parts of the heart relative to the anterior chest wall. Records were obtained from hearts placed in a water bath after death. Tracings from the left atrium of normal subjects and of patients with mitral valvular disease were discussed. By means of recently developed electronic equipment, such tracings could be recorded with an oscillograph simultaneously with the electrocardiogram or any other monitoring parameter. Large thrombi or tumors of the left atrium, simulating mitral stenosis by a valve-like action, may be recognized by this method. Pericardial effusion yielded a pathognomonic tracing by altering the distances between the reflecting planes.

BRACHFELD

**Ghazi Vakili, R., and Chatillion, J. Y.: The Delay of Arterial Ejection over the Neck and over the Carotids in Complete Left Bundle Branch Block.** Cardiologia 34: 28, 1959.

In 15 patients with left bundle-branch block and in 15 control individuals both carotid pulses were recorded with the aid of a Marey capsule; the "global" neck pulse was recorded with the use of a pneumatic cuff placed around the neck and inflated to a pressure of 10 to 15 mm. Hg. The well-known delayed onset of arterial ejection in cases of left bundle-branch block was observed. The interval from the beginning of the QRS to the onset of arterial ejection at the neck was 0.15 to 0.26 second in patients with complete left bundle-branch block. These values agreed well with those found by others. The use of this approach to the elucidation of doubtful cases of conduction disturbances is stressed.

BRACHFELD

**Von Planta, P., Schweizer, W., Batschelet, E., and Pletscher, A.: Tobacco and the Circulation. I. A method for Evaluation of Antinicotinic Substances.** Cardiologia 34: 34, 1959.

In 320 subjects, alterations of the ballistocardiogram, pulse rate and arterial pressure were studied. The ballistocardiogram showed deterioration after smoking in 19 per cent of the subjects; the highest degree of such alterations was in the groups aged 30 to 60. Inhalation of the cigarette smoke caused an increase in pathologic alterations of the ballistocardiogram. The reaction of the ballistocardiogram to smoking was not dependent on the presmoking pattern. Pathologic alterations were observed equally in the ballistocardiogram of men and women. Repetition of the smoking test caused the same alterations in 89 per cent of the individuals. Pulse rate and arterial pressure changed significantly after smoking; decrease and increase of these parameters were observed to almost the same degree. The effect of nicotine is detectable with the use of the ballistocardiogram. This method seems more suitable for testing antinicotinic substances than the pulse rate or the arterial pressure.

BRACHFELD

## HYPERTENSION

**Newcombe, C. P., Shucksmith, H. S., and Suffern, W. S.: Sympathectomy for Hypertension.** Brit. M. J. 1: 142 (Jan. 17), 1959.

The results of sympathectomy in 212 patients suffering from hypertension were reported. The extent of the operative procedure used varied according to the recognized established procedures. In general more extensive procedures were used for the younger patients in whom symptoms were more evident, and the smaller operations were used for the older and less symptomatic patients. In 376 operations performed on the 212 patients there were 9 deaths within 6 weeks of the operation. The 10-year survival rate in this series was 66 per cent and the 5 year rate was 76 per cent. Reduction of the diastolic pressure by 15 to 45 mm. Hg after the procedure occurred in nearly all the patients for some weeks or months but only in 27 per cent was a reduction of more than 15 mm. Hg maintained. Retinal improvement resulted in 49 per cent with severe changes, and when there was no improvement in advanced retinal degeneration, death was not too long delayed. In general, sympathectomy resulted in symptomatic relief and gave many patients an increased expectation of a full and active life.

KRAUSE

**Moyer, J. H., and Beem, J.: Treatment of Hypertension in the Ambulatory Patient.** Am. J. Cardiol. 3: 199 (Feb.), 1959.

The primary object in treating the hypertensive patient is to lower the blood pressure by the simplest means possible to levels as near normal as can be well tolerated. The vascular deterioration, especially of the kidney, which progresses in the presence of sustained hyper-

tension is well illustrated and provides the rationale for antihypertensive therapy. In mild to moderate cases, the authors began treatment with chlorothiazide 1 to 2 Gm. per day. For a more potent hypertensive effect a Rauwolfia preparation was added; and, if needed, hydralazine was added in doses up to 400 mg. daily. In severe hypertensive patients, with diastolic pressures of over 140 mm. Hg or over 120 mm. Hg in the presence of vascular complications, a ganglionic-blocking agent was promptly "titrated" in the patient who was receiving a baseline therapy of chlorothiazide plus Rauwolfia. Reserpine or rescinnamine (2.5 to 5 mg. intramuscularly every 6 hours) was used in emergencies. The roles of emotional factors, sodium restriction, and of other agents were described in presenting the broad view required in the proper management of the hypertensive patient.

ROGERS

**Sears, H. T., Snow, P. J. D., and Houston, I. B.: Treatment of Hypertension with Pentolinium and Mecamylamine.** Brit. M. J. 1: 462 (Feb. 21), 1959.

The authors describe their experiences with 78 severely hypertensive patients treated with pentolinium and mecamylamine over a 4-year period. The ability to lower blood pressure was not the only criterion by which these drugs were evaluated. The following factors were also considered; subjective improvement, production of side effects, reversal of eyeground changes, and the survival period. Side effects, which occurred with both preparations, were more numerous with mecamylamine and in the authors' opinion these effects outweighed the advantage of its more constant absorption. In many patients the concomitant use of reserpine permitted the dose of the ganglionic-blocking agents to be reduced, with resultant decrease in the severity of side effects. In general both drugs (pentolinium and mecamylamine) were valuable in the treatment of severe hypertension and participated in prolonging life and restoring or preserving sight.

KRAUSE

**Grody, M. H.: Antihypertensive Drugs in Toxemia: A Practical Integrated Plan of Management.** Obst. & Gynec. 13: 166 (Feb.), 1959.

A plan is outlined for the management of the toxemia of pregnancy based upon its degree of severity. The combination of parenteral hydralazine and reserpine is most popular in severe cases. Protoveratrine is held in reserve if the desired effect is not obtained with this combination. In milder cases, the combination of reserpine and chlorothiazide is recommended. Generally the vasodepressor drugs initially decrease the output of urine. This situation becomes serious only when it results in progressive retention of nitrogenous products or renal failure. The decrease in urinary output is secondary to increased reabsorption of water by the renal tubules. As a rule it is temporary and is soon followed by polyuria. If a patient is unusually sensitive to the action of hypertensive drugs, it is important to be aware of a method to combat a true hypotensive state of shock. Norepinephrine in such instances will usually promptly return the blood pressure to normal. A word of caution relative to the use of barbiturates in eclampsia or severe preeclampsia is added. These drugs depress the higher centers and may further reduce cerebral blood flow, which is already compromised by cerebral vasoconstriction. The ultimate effect is an even greater decrease in oxygen consumption by the brain. The author suggests the immediate use of intravenous hydralazine during a convulsion rather than the use of a barbiturate.

KRAUSE

**Freis, E. D.: Treatment of Hypertension with Chlorothiazide.** J.A.M.A. 160: 105 (Jan.), 1959.

The concomitant use of chlorothiazide allows lower and less toxic dosages of other hypertensive agents in controlling blood pressure. The drug does not reduce blood pressure in normotensive subjects although it induces the same increase in salt excretion as in hypertensive patients. In adding chlorothiazide to the regimen of a patient taking ganglionic-blocking agents the dosage of the latter must be reduced, usually by half. Patient responsiveness is so increased by chlorothiazide that in full dosage a severe hypotension including postural collapse may occur. The complications of chlorothiazide therapy are not common but awareness will aid in their prevention: the value of this drug far outweighs its harm. The so-called toxic reactions to chlorothiazide are extensions of its fundamental saluretic and kaluretic actions. Hypopotassemia is frequent, and potassium supplements should be used when this develops.

KITCHELL

**Folkow, B., Grimby, G., and Thulesius, O: Adaptive Structural Changes of the Vascular Walls in Hypertension and Their Relation to the Control of Peripheral Resistance.** Acta. physiol. scandinav. 44: 255, 1958.

The functional importance of an increased wall to lumen ratio due to renal hypertrophy of the resistance vessels in hypertensive disease was evaluated by comparing the vascular resist-

ance in 25 normal and 34 hypertensive subjects when the vessels were brought to an absolutely maximal dilatation. This was accomplished by increasing the ischemia of the vessels of the forearm by means of a venous occlusion plethysmograph which measured blood flow and occluded the vessels by a proposed pressure. Increasing amounts of work on the forearm muscles during the last minute of ischemia were also used. Lastly, to augment the dilator influence, the plethysmograph permitted the circulation of warm water at a temperature of 43 C., which was maintained by means of a hot-air stream from an electric fan. Six of the 25 normotensive subjects were studied when brought to a state of acute hypertension by means of a steady intravenous infusion of norepinephrine in amounts sufficient to raise the mean blood pressure about 30 per cent. It was found that the vessels promptly dilate both in normotensive and hypertensive subjects and an almost maximum dilatation was reached after only 5 minutes of ischemia in both groups. The resistance to flow for the 5 normotensive subjects during acute hypertension was found to be the same at the 2 perfusion pressure levels. It is believed by the authors that a given level of smooth muscle tone will probably result in a higher flow resistance in hypertensive disease, where hypertrophy of the vascular wall has taken place but that this rise in vascular tone may be due to local influences on the resistance vessels.

RINZLER

**Weller, J. M., and Hoobler, S. W.: Salt Metabolism in Hypertension.** Ann. Int. Med. 50: 106 (Jan.), 1959.

A number of aspects of sodium chloride metabolism in patients with essential hypertension are reviewed. It is suggested that the increased content of sodium and water found in the arterial wall of hypertensive patients and animals with experimental hypertension may be responsible for the elevation of blood pressure either by narrowing the arteriolar lumen or by increasing the reactivity of its smooth muscle. The effects of chlorothiazide in the treatment of edema and hypertension are discussed. It is suggested that chlorothiazide may reduce blood pressure in some instances by depleting plasma and extracellular fluid volume and, in others, by a redistribution of body sodium and water. The major effect of chlorothiazide may be to reduce the increased sodium and water content of the vascular smooth muscle in the hypertensive patient. This would decrease peripheral resistance and produce a fall in blood pressure without any change in extracellular fluid volume.

KAYDEN

**Short, D S.: Arteries of Intestinal Wall in Systemic Hypertension.** Lancet 2: 1261 (Dec. 13), 1958.

The arterial bed of the small intestine was studied by means of postmortem arteriography with a bismuth gelatin suspension. Complete filling of the submucosal arteries down to 0.05 mm. was obtained in 6 cases of hypertension and 6 control specimens. A decreased number of vessels in the intestinal wall and more abrupt tapering of the lumen were demonstrated in 4 of the 6 hypertensive patients. Histologic examination showed only infrequent slight intimal thickening in the submucosal arteries and no definite medial hypertrophy. It is suggested that in established hypertension the submucosal arteries of the small intestine are in a state of diffuse structural narrowing.

KURLAND

## METABOLIC EFFECTS ON CIRCULATION

**Szekeres, L. and Schein, M.: Cell Metabolism of the Overloaded Mammalian Heart in Situ.** Cardiologia 34: 19, 1959.

The metabolism of the acutely failing rat heart, produced by constricting the ascending aorta, was studied. The changes in cardiac metabolism were characterized by impairment of energy production and were similar to those of acute anoxia. The synthesis of high-energy phosphates was decreased; oxidative as well as anerobic processes involved in energy production were found to be depressed. It seems possible that myocardial anoxia (probably of the stagnant type) is also responsible for the disturbance in cardiac energy production in cases of experimental heart failure.

BRACHFELD

**Cookson, H.: The Thyroid and the Heart.** Brit. M. J. 1: 254 (Jan. 31), 1959.

Hyperthyroidism should always be suspected when atrial fibrillation is present, particularly if a rheumatic, coronary, or hypertensive etiology is not apparent. A clue to the diagnosis is the inability to slow the ventricular response with digitalis, particularly in the older age group. An increased pulse pressure is an additional valuable clue to the diagnosis of hyperthyroidism. The treatment for failure with fibrillation

is the use of digitalis and diuretics combined with an antithyroid drug. After several weeks, if sinus rhythm has not returned, the use of quinidine may convert the fibrillation to a normal sinus mechanism. The clinical expression and the cardiac and electrocardiographic signs of myxedema are in many ways the antithesis of hyperthyroidism. The characteristic electrocardiogram shows a slow, low voltage, and a flattening of the T waves. Exceptions naturally occur; for example, a previously hypertensive patient (now myxedematous) may have an electrocardiogram with left ventricular hypertrophy. In general the myxedema electrocardiogram shows changes in all leads. In the roentgenologic appearance of the myxedema heart it is probably true that enlargement is almost always due to pericardial effusion. This "enlargement" usually disappears with proper thyroid therapy.

KRAUSE

**Newman, D. A.: Reversal of Intractable Cardiac Edema with Prednisone.** New York State J. Med. **59**: 625 (Feb. 15), 1959.

Various causes of intractable heart failure are discussed and several methods to reverse the refractory state are presented. When factors other than those directly related to heart failure are eliminated and the usual methods to control the failure have failed, the use of steroids has been suggested. The neurohypophysis and the aldosterone-producing adrenal glands play a major role in this failure of the homeostatic adjustment mechanisms. This failure results in the extracellular fluid electrolytes. Ten patients with cardiac edema and normal serum electrolytes became unresponsive to the commonly used diuretic measures, including mercurials, and attempts to produce hyperchloremia and acidosis. In 8 patients the refractoriness was reversed by the use of prednisone in a specified manner and dosage. This was probably accomplished by the promotion of transcellular and transcompartmental shifts of electrolytes from an electrolyte pool.

KRAUSE

**Davis, J. O., Kliman, B., Yankopoulos, N. A., and Peterson, R. E.: Increased Aldosterone Secretion Following Acute Constriction of the Inferior Vena Cava.** J. Clin. Invest. **37**: 1783 (Dec.), 1958.

Adrenal vein plasma concentration of aldosterone, corticosterone and Porter-Silber steroids was studied in dogs subjected to acute constriction of either the thoracic or the abdominal vena cava. Within 30 minutes after a ligature previously placed around the thoracic inferior vena cava had been tightened, aldosterone secretion in adrenal vein plasma reached levels 2 to 4 times greater than control values, while corticosterone and Porter-Silber reacting steroid output decreased in 3 of the 4 animals studied. During the period of time that the ligature was in place, inferior vena caval pressure rose 8 to 13 cm. of water while arterial pressure, adrenal blood flow and plasma volume fell without any consistent change being observed in plasma sodium or potassium concentration. When dextran was infused into 3 similarly prepared dogs at a rate which increased the plasma volume 44 to 330 per cent, a comparable increase in aldosterone secretion rate was noted. In 4 animals the abdominal vena cava was constricted at a level above the adrenal veins and in 2 of these dogs the aldosterone output rose when the pressure in the vena cava increased to levels greater than 14 cm. of water above control value. When the pressure elevation was not sustained at a high level, the aldosterone output either remained unchanged or decreased. The levels of corticosterone and Porter-Silber steroids did not show consistent changes. The authors believe that the data presented demonstrate the acuteness of adrenal cortical response with reference particularly to aldosterone secretion following an alteration in cardiovascular function. The mechanism responsible for the changes however remains obscure. Since corticosterone output decreased as aldosterone output increased, it was thought that increased ACTH secretion was not involved, while the dextran experiments indicated that loss of vascular volume alone was not responsible.

FREEDBERG

**Weisberg, R. I., and Sampson, J. J.: Determinations of Serum Enzymes in Surgical Patients: Value in Diagnosis of Complicating Myocardial Infarction.** Am. Heart J. **57**: 240 (Feb.), 1959.

Preoperative and postoperative determinations of serum glutamic oxalacetic transaminase, serum lactic dehydrogenase, and serum glutamic pyruvic transaminase were performed in 21 surgical patients. No significant changes were found. This limited series thus indicates that surgical procedures by themselves, including major operations with skeletal muscle incision and dissection, will not cause sufficient elevations of these serum enzymes to mask the characteristic curve of myocardial infarction when it complicates the operative or postoperative course.

SAGALL

## PATHOLOGY

**Brewer, D. B., and Heath, D.: Pulmonary Vascular Changes in Eisenmenger's Complex.** J. Path. & Bact. **77**: 141 (Jan.), 1959.

Detailed histologic observations on the pulmonary vascular changes that occurred in 4 patients with Eisenmenger's complex are presented. The primary vascular changes were medial hypertrophy of the small muscular pulmonary arteries, the development of a distinct muscular media between the internal and external elastic lamina in vessels less than 100 micra in diameter, and fibroelastosis of the intima causing thickening or complete occlusions. Secondary compensatory changes, which presumably maintained an adequate blood flow through the pulmonary capillaries, were the formation of thin-walled dilated branches of the muscular pulmonary arteries; these branches arise proximal to the sites of arterial obstruction and end as capillaries in the alveolar walls. In 1 patient there were many demonstrable anastomoses between the pulmonary arteries and the bronchial circulation and also between the pulmonary arteries and the pulmonary veins. No significant degree of hemosiderosis was seen, probably because the pulmonary venous pressure was not elevated in these patients.

KARPMAN

**Ruiter, M., and Hadders, H. N.: Predominantly Cutaneous Forms of Necrotizing Angiitis.** J. Path. & Bact. **77**: 71 (Jan.), 1959.

Two groups of necrotizing angiitis entirely or chiefly limited to the skin were investigated by histologic examinations. One group of cutaneous eruptions known clinically as arteriolitis allergica cutis was distinguished by exudative vascular reactions (all of approximately the same age) associated with swelling of the endothelial cells, fibrinoid changes in the vessel wall, and inflammatory infiltrates. The cutaneous type of periarteritis nodosa revealed fibrinoid swelling of the intima and fibrinoid necrosis in addition to inflammatory infiltrates: simultaneous exudative and reparative processes were often seen in a single section. Allergy in the personal or family history was often present in patients with arteriolitis allergica cutis but not in those with periarteritis nodosa. This may be a significant observation, for it was noted that eosinophils were lacking in most cases of cutaneous periarteritis nodosa whereas they were seldom absent in arteriolitis allergica cutis.

KARPMAN

## PHARMACOLOGY

**Vick, R. L: Effects of Some Steroid and Nonsteroid Lactones on Potassium Exchange and Physiological Properties of the Isolated Perfused Guinea Pig Ventricle.** J. Pharmacol. & Exper. Therap. **125**: 40 (Jan.), 1959.

This article reports the effects of 2 cardiac glycosides, crystalline ouabain U.S.P. and dihydro-ouabain, and 3 nonsteroid lactones, $\beta$-angelicalactone, patulin, and pulvinic acid dilactone on the function and the potassium balance of the isolated, perfused guinea pig ventricle preparation. Ouabain and dihydro-ouabain produced positive inotropic effects in all concentrations used. Patulin in sufficiently high concentrations caused a brief increase in contraction height followed by a return to the hypodynamic level. In lesser concentrations it did not alter contraction height. Alpha-angelicalactone and pulvinic acid dilactone in sufficiently high concentrations caused only negative inotropic effects. All the lactones caused contracture, the extent of which varied with the concentration. In the case of the steroid lactones, contracture occurred only with concentrations higher than those necessary to restore contraction height to normal, while the nonsteroid lactones caused contracture in concentrations that did not alter the height of contraction. All the lactones caused the ventricles to lose potassium to the perfusate. Small concentrations of dihydro-ouabain caused only an initial loss, after which the ventricles were in potassium balance.

RINZLER

**Ford, R. V., Rochelle, J. B., III, Bullock, A. C., Spurr, C. L., Handley, C., and Moyer, J. H.: Laboratory and Clinical Observations on Chlorazanil, a Nonmercurial Orally Effective Diuretic Agent.** Am. J. Cardiol. **3**: 148 (Feb.), 1959.

Chlorazanil (Daquin, Orpidan, Neo-Urofort) is a triazine derivative, the diuretic potency of which depends on an N = C — N group. The present study of its pharmacologic value in dogs and in man gave results similar to those previously obtained. Given orally in a dose of 300 to 600 mg. its action was evident within 2 hours and continued for approximately 18 hours. Urinary excretion of water, sodium, chloride, bicarbonate, and potassium were increased in descending order of magnitude. The potency of 600 mg. of the drug, in terms of natriuresis, was equivalent to that of 1 ml. of meralluride. Its action was not appreciably altered by the concomitant administration of theophylline in dogs. Repeated doses were effective and, after

days of therapy, serum electrolyte levels had ot changed significantly. However, in some pa- ents chronic therapy was associated with evi- nce of diminution in glomerular filtration rate. lthough the mechanism of action of chlorazanil as not clear, it appeared to differ from that of etazoleamide or of organomercurial agents.

ROGERS

**ichel, D.: The Influence of Cardiac Glycosides on Interval between the Second Heart Sound and the Opening Snap of the Mitral Valve.** Ztschr. Kreislaufforsch. **48:** 107 (Feb.), 1959.

A single intravenous injection of 0.25 mg. of trophanthin K or 0.5 mg. of digoxin in 23 atients with mitral stenosis and sinus rhythm ed in all instances to an increase in the interval etween the second sound and the mitral open- ng snap. This increase averaged 33 per cent and was greater in decompensated than in com- pensated patients. It showed no correlation with the changes in heart rate, cardiac output or venous pressure. At the same time, the interval from QRS to the first heart sound showed a progressive decrease. These changes were at- tributed to a decrease in left atrial pressure, and could be caused by a more forceful atrial contraction, or decreased pulmonary blood vol- ume. These results, which were similar to those obtained in left ventricular failure, indicated that digitalis therapy had a favorable effect also on patients with mitral stenosis without heart failure.

LEPESCHKIN

**Haddy, F. J., Gordon, P., and Emmanuel, D. A.: The Influence of Tone upon Responses of Small and Large Vessels to Serotonin.** Circulation Research **7:** 123 (Jan.), 1959.

The infusion of small doses (10 γ/min.) of serotonin into the brachial artery of the dog resulted in a decrease in total forelimb resist- nce when the resistance was high, no change when the resistance was intermediate, and an increase when the resistance was low. The vas- ular tone was varied by denervation of the forelimbs or by bilateral vagotomy. The bidirec- tional responses to serotonin resulted from the fact that neurogenic factors changed small ves- el calibers without altering the caliber of large vessels and serotonin dilated small vessels at he same time that it constricted large vessels. When vascular tone was varied by humoral gents, including intraarterial infusion of metha- holine or levarterenol, the bidirectional response o serotonin was difficult to demonstrate.

PAUL

**Waud, D. R., Kottegoda, S. R., and Krayer, O.: Threshold Dose and Time Course of Norepinephrine Depletion of the Mammalian Heart by Reserpine.** J. Pharmacol. & Exper. Therap. **124:** 340 (Dec.), 1958.

The authors demonstrate that the heart-rate-increasing effect of a challenging dose of 3 mg. of reserpine given to the heart-lung preparation of the dog is a reliable measure of the cardiac content of intrinsic sympathomimetic catechol amines, especially norepinephrine. Hexamethonium does not prevent the release of norepinephrine in the heart-lung preparation. In a single intraperitoneal dose of 100 μg./Kg. reserpine can deplete the heart of norepinephrine in 24 hours with no side effects. By 10 to 20 days normal stores of norepinephrine are found. Some accumulation has begun by the sixth day.

RINZLER

**Ford, R. V., and Rochelle, J. B., III.: The Differing Mechanisms of Action of Mercurials, Carbonic Anhydrase Inhibitors, and Chlorothiazide as Diuretic Agents.** J. Lab. & Clin. Med. **53:** 53 (Jan.), 1959.

This study was designed to explore the concept that the mechanism of action of certain diuretics are either competitive or noncompetitive when administered simultaneously. Subjects were men with well-controlled congestive heart failure due to hypertensive cardiovascular disease who were edema free at the time of the study. The patients were given an initial water load, drank a stated volume of water throughout the study period, and were given intravenous isotonic saline throughout the study period. Meralluride, acetazolamide, and chlorothiazide were the 3 diuretic agents studied and all were administered intravenously. When given in combination, doses of equal potency in terms of sodium excretion were used. It was found that sodium excretion, which was increased by the administration of meralluride, could be further enhanced by the subsequent administration of acetazolamide. Conversely, natriuresis was produced with the initial administration of acetazolamide and increased with the subsequent administration of meralluride. When meralluride was followed by chlorothiazide, the initial response to the first agent was increased by the second, but when the order was reversed so that chlorothiazide was given first, no further natriuresis could be induced by the administration of meralluride. Similarly, administration of acetazolamide first followed by chlorothiazide resulted in an increased sodium excretion both after the first and second agents, whereas, when chlorothiazide preceded the aceta-

zolamide, sodium excretion was not increased by the second agent. In another study when meralluride and acetazolamide were given initially, producing sodium excretion greater than either of the 2 agents alone, the addition of chlorothiazide resulted in an even greater sodium excretion.

MAXWELL

**Innes, I. R., Krayer, O., and Waud, D. R.: The Action of Rauwolfia Alkaloids on the Heart Rate and on the Functional Refractory Period of Atrio-Ventricular Transmission in the Heart-Lung Preparation of the Dog.** J. Pharmacol. & Exper. Therap. **124**: 324 (Dec.), 1958.

This study deals with the effects of 10 rauwolfia preparations on the heart rate, the functional refractory period of atrioventricular transmission and the A-V propagation time. The heart-lung preparation of the dog was used and a comparative study was made of the action of the different types of rauwolfia alkaloids on normal and reserpine-pretreated dog. Two distinct groups were found. The first, consisting of ajmaline, serpentine, aricine, reserpine and α-yohimbine, caused a decrease in heart rate and a prolongation of the functional refractory period of A-V transmission and of the A-V propagation time. The second, consisting of raunescine, isoraunescine, deserpidine, reserpine and rescinnamine, at first increased the heart rate and shortened the functional refractory period and the A-V propagation time. After 1½ to 2½ hours, with a dose equivalent in effect to 3 mg. of reserpine, the heart rate slowed while the other 2 modalities returned toward their control duration or were frequently further prolonged. When the heart-lung preparation was first depleted of intrinsic sympathomimetic amines by previous treatment with reserpine, the drugs in the second group lacked this transient cardioaccelerator action and facilitating action on A-V transmission.

RINZLER

**Lown, B., Marcus, F., and Levine, H. D: Digitalis and Atrial Tachycardia with Block: A Year's Experience.** New England J. Med. **260**: 301 (Feb. 12), 1959.

In the year 1957, 32 episodes of paroxysmal atrial tachycardia with block were diagnosed electrocardiographically in 23 patients. In 24 episodes the etiologic factor was digitalis intoxication resulting from either overdosage of the drug, a mercurial-induced diuresis, or increased sensitivity to digitalis. The patients in whom this rhythm appeared were usually in an advanced state of chronic cardiac decompensation and had been subjected to a rigid sodium restriction. Often no striking change in symptom developed in association with the arrhythmi and the abnormal rhythm was detected only b the electrocardiogram. The atrial rate in th series ranged from 138 to 250, with a mean 176. The degree of atrioventricular block varie greatly. The atrial complex frequently was d minutive and difficult to distinguish except the right precordial leads. When present in t limb leads, the P wave was invariably uprig in lead II. Carotid sinus stimulation increas the degree of atrioventricular block but did n alter the atrial rate. The rhythm was most fr quently confused with atrial flutter, but al simulated other rapid supraventricular rhythm In 4 of the 24 episodes due to digitalis ove dosage, a normal mechanism was restored simpl by discontinuing digitalis and diuretic measure Digitalis was continued in 2 patients and bot died. In the remaining 18 patients addition measures were necessary; of this group 5 ep sodes were controlled by the oral or intravenou use of potassium, 10 by the combined use o potassium and procaine amide, and 3 by procain amide alone.

SAGALL

**Killen, D. A., Lance, E. M., and Owens, G.: Relative Suitability of Urokon 70 Per Cent and Hypaque 90 Per Cent for Use as Aortographic Contrast Media.** Surgery **45**: 436 (Mar.), 1959.

The tissue toxicity of Urokon 70 per cent and Hypaque-M 90 per cent was assessed in dogs. This was limited to an evaluation of their effect on the spinal cord and kidney, as damage to these organs has been the cause of over 50 per cent of the serious complications resulting from the clinical use of Urokon 70 per cent in abdominal aortography. These substances contain comparable amounts of iodine and are of the same radiopacity. The osmolarity and pH are also similar. Hypaque is somewhat less soluble and has to be warmed to body temperature before injection. Hypaque is significantly more viscous than Urokon. Urokon produced paraplegia in nearly all the animals tested, regardless of whether the medium was injected into the aorta or into the first pair of lumbar arteries caudad to the origin of the left renal artery. Hypaque on the other hand was not associated with any paraplegia in doses up to 15 times tha used with Urokon. There was marked necrosi of the gray matter of spinal cord, but minima evidence of vascular involvement in the form o thrombosis. Of the animals receiving intra-aorti Urokon, only 3 survived 48 hours. All 3 devel oped azotemia. No animal receiving Hypaqu

became uremic. There was injury to the tubular epithelium but no evidence of thrombosis. These studies indicate that the mechanism of Urokon injury to the spinal cord and kidney is a direct cytotoxic effect. Hypaque-M 90 per cent exhibited much less neurotoxicity and nephrotoxicity than Urokon 70 per cent. However, the greater viscosity of Hypaque impairs its angiographic effectiveness when manually injected into the aorta through the small bore injection equipment used for translumbar aortography.

SHEPS

**Vander, A. J., Malvin, R. L., Wilde, W. S., and Sullivan, L. P.: Localization of the Site of Action of Chlorothiazide by Stop-Flow Analysis.** J. Pharmacol. & Exper. Therap. **125**: 19 (Jan.), 1959.

The technic of "stop-flow" analysis has been used to compare proximal and distal tubular function in dogs before and after administration of chlorothiazide. After chlorothiazide the ability of the proximal tubule to reabsorb water during stopped flow was reduced. Proximal reabsorption of sodium and potassium was reduced in such amounts that the concentrations of these substances in the fluid reabsorbed from the proximal tubule during occlusion did not change but remained plasma-like. Chlorothiazide increased distal tubular potassium secretion. The data on distal potassium reabsorption were less clear-cut, but chlorothiazide appeared to have some inhibitory effect upon distal potassium reabsorption. Chlorothiazide exerted no effect on the distal capacity to lower sodium concentration during stopped flow.

RINZLER

**Hess, M. E., and Schmidt, C. F.: Cardiovascular Effects of Chloroquine with Special Reference to Its Antifibrillatory Action.** Circulation Research **7**: 86 (Jan.), 1959.

Intravenous injections of chloroquine in doses of 0.2 to 1.5 mg. per Kg. are capable of terminating aconitine-induced atrial fibrillation in the open-chest dog preparation. Intravenous chloroquine (2 mg. per Kg.) had little effect on the systemic blood pressure, despite its marked vasodilating action on intraarterial administration and a depressant effect on ventricular contraction. In contrast, comparable doses of quinidine produced a marked fall in systemic blood pressure. Chloroquine and quinidine were equally effective in depressing the resting excitability of the isolated cat papillary muscle; however, chloroquine, in contrast to quinidine, decreased conduction velocity very little. The muscle recovered from chloroquine-induced depression but showed little recovery from the quinidine effects. These attributes of chloroquine suggest its usefulness in the treatment of clinical arrhythmias.

PAUL

## PHYSICAL SIGNS

**Schlitter, J. G., and Scholmerich, P.: The Summation Gallop Rhythm.** Ztschr. Kreislaufforsch. **47**: 1081 (Dec.), 1958.

The diastolic gallop sound resulting from the summation of the third heart sound and the atrial sound was found in 14 per cent of all phonocardiograms, usually in the 35 and 70 c.p.s. range. It appeared when the P wave happened to begin 0-0.7 second after the end of the preceding T wave; this took place in sinus tachycardia, wandering pacemaker, supraventricular extrasystoles, and A-V block (complete, 2.1 or Wenckebach type). In some patients only the atrial sound of the third heart sound was present when this time relation was not met. The gallop sound was considered to originate when rapid ventricular filling in early diastole became even more rapid because atrial systole occurred at the same time. Appearance of the gallop in sinus tachycardia of adults usually indicated latent or manifest cardiac failure.

LEPESCHKIN

**Burnard, E. D.: The Cardiac Murmur in Relation to Symptoms in the Newborn.** Brit. M. J. **1**: 131 (Jan. 17), 1959.

A cardiac murmur was often heard in the newborn during the first few hours of life. This murmur was usually crescendo, at the end of systole, and sometimes it continued through the second sound. It was probably due to flow through a persistent ductus arteriosus. A direct relationship to rectal temperature and to asphyxia at birth was demonstrated in the mature babies. In premature babies the incidence was equal to that of mature babies after birth asphyxia. The murmur accompanied dyspnea in premature babies and in severely breathless mature babies. When mature babies had suffered birth asphyxia a raised respiratory rate was evident though they appeared healthy. The murmur was present in 75 per cent. A reduction in rectal temperature seemed to result in relief of dyspnea and disappearance of murmur. Conversely, warming 3 babies shortly after birth brought about dyspnea as well as the murmur. These data complement the hypothesis that there may be changes in blood flow through the great vessels, consequent on temperature changes, which influence the genesis of the murmur.

KRAUSE

## PHYSIOLOGY

**Woods, E. F., and Richardson, J. A.: Effects of Acute Anoxia on Cardiac Contractility.** Am. J. Physiol. **196**: 203 (Jan.), 1959.

Ventricular contractile force and arterial blood pressures were measured in anesthetized, vagotomized dogs rendered hypoxic by respiration with 100 per cent nitrogen. Marked increments in heart force and blood pressures were observed during brief nitrogen exposure and during the period of reoxygenation following substitution of room air for nitrogen. Experiments in animals subjected to bilateral adrenalectomy, thoracic sympathectomy, and total preganglionic sympathetic block indicated that the responses to acute oxygen lack were mainly due to stimulation of the sympathetic nervous system, while the responses to reoxygenation were dependent upon both the adrenal medulla and the sympathetic nerves.

KAYDEN

**Pauli, H. G., Noe, F. E., and Coates, E. O.: Central Regulation of the Respiration in Cardiac Patients.** Cardiologia **34**: 114, 1959.

The ventilatory response to increasing carbon dioxide tension was studied by means of a rebreathing method in 20 cardiac patients. Compared to the findings in 11 normal subjects, there was a lowered central threshold for carbon dioxide stimulation, whereas central respiratory responsiveness remained practically unchanged. Central responsiveness was determined by the slope of the carbon dioxide tension—ventilation curve. The 7 patients with predominant mitral stenosis in this group were characterized by a significant depression of central responsiveness. Their total ventilation was nevertheless higher than normal, because of the extreme lowering of the threshold for carbon dioxide stimulus.

BRACHFELD

**Howell, C. D., Horvath, S. M., and Ferrand, E. A.: Evaluation of Variability in the Cardiac Output of Dogs.** Am. J. Physiol. **196**: 193 (Jan.), 1959.

The cardiac output was calculated by the Fick principle in 245 adult dogs. The mean cardiac output was 2.36, and the range from 0.91 to 5.09 liters per minute. Determination of cardiac output using venous blood from the right atrium was not significantly different from the mean of all determinations. The 6 groups of dogs, based on different sources of arterial and venous blood, differed from each other in unpredictable ways, suggesting that the physiologic measurements obtained between 60 and 90 minutes after anesthesia were subject to great variation, but that cardiac output was no more variable at this time than other physiologic measurements. The cardiac output of these anesthetized dogs was found to have a low correlation with body weight.

KAYDEN

**Costantin, L. L.: Effect of Pulmonary Congestion on Vagal Afferent Activity.** Am. J. Physiol. **196**: 49 (Jan.), 1959.

Pulmonary venous occlusion was shown to increase the activity of slowly adapting pulmonary stretch receptors by mechanical alterations within the lung parenchyma. Two types of response were evident: stimulation throughout the respiratory cycle and stimulation only during low lung volumes. Pulmonary arterial occlusion caused both significant increases and decreases in fiber activity. Two fibers demonstrated cardiac-triggered impulses superimposed upon a basic respiratory rhythm, an effect dependent upon pulsation of the pulmonary arterial tree. The results of this investigation indicated a 2-fold responsiveness of the pulmonary stretch receptors, i.e., to the volume of air in the lungs and, to a lesser extent, to the degree of distention of the pulmonary vasculature. The latter effect was suggested as an important factor in the decreased depth of respiration during pulmonary congestion.

KAYDEN

**Love, W. D., and Burch, G. E.: Influence of the Rate of Coronary Plasma Flow on the Extraction of $Rb^{86}$ from Coronary Blood.** Circulation Research **7**: 24 (Jan.), 1959.

The myocardial uptake of $Rb^{86}$ was studied in dogs by measuring the extraction of $Rb^{86}$ from arterial plasma during 1 passage through the myocardium. The extraction of isotope by the myocardium was found to be logarithmically related to coronary plasma flow. The maximum extraction in very low coronary plasma flows approached 85 per cent rather than 100 per cent, and this observation was interpreted as supporting the concept that anatomic or functional shunts of plasma exist within the myocardium. It was suggested that estimates of the rate of coronary plasma flow can be made in man without cardiac catheterization, if myocardial radioactivity can be measured accurately with an external monitor.

PAUL

**Manzotti, M.: The Effect of Some Respiratory Maneuvers on the Heart Rate.** J. Physiol. 144: 541 (Dec. 30), 1958.

The effect of various respiratory maneuvers on the heart rate was studied in normal young male subjects and in anesthetized cats and rats. A sinus arrhythmia was noted to occur normally in man with quiet respiration. During voluntary positive-pressure breath-holding the heart rate gradually increased (after an initial short period where the response was unpredictable) and then remained at that level during the rest of the breath-holding period. With a negative-pressure breath-holding maneuver, the heart rate fell below the initial value and then returned approximately to the starting rate. Correlations were derived between various positive intrapulmonary pressures and the heart rate; no correlation was found between the various negative intrapulmonary pressures and the heart rate. The response of the heart rate to passive variations of the intrapulmonary pressures in animals was completely different from that in man. It is suggested that the aortic baroceptors represent the sensory area for the blood-flow heart rate reflex and that the variations in blood flow occur at the level of the pulmonary circulation and are brought about by respiratory maneuvers.

KARPMAN

**Hoffman, B. F., de Carvalho, A. P., Mello, W. C., and Cranefield, P. F.: Electrical Activity of Single Fibers of the Atrioventricular Node.** Circulation Research 7: 11 (Jan.), 1959.

The authors have investigated the nature and cause of delay in the propagation of excitation from atrium to ventricle. Multiple intracellular microelectrodes were used to obtain simultaneous records from single fibers of atrium, A-V node and His bundle in the rabbit heart. Measurements of conduction times demonstrated that the slow spread of the impulse near the atrial border of the A-V node caused the major portion of the atrioventricular delay. The conduction velocity fell from 0.8 to 1 M. per second outside this critical region to 0.05 to 0.02 M. per second at the border of the A-V node. Furthermore, in cells in this area, the recorded action potentials showed consistent differences and were characterized by a tendency to have a notched upstroke, slow rate depolarization, low amplitude, and a low resting potential. The authors suggested that conduction in the node was decremental, implying that the action potential appeared to diminish progressively in amplitude and rate of depolarization.

PAUL

**Hogancamp, C. E., Kardesch, H., Danforth, W. D., and Bing, R. J.: Transmembrane Electrical Potentials in Ventricular Tachycardia and Fibrillation.** Am. Heart J. 57: 214 (Feb.), 1959.

Observations of the electrical and mechanical events that follow the induction of ventricular tachycardia and ventricular fibrillation in the isolated guinea pig by aconitine are reported. Individual myocardial fibers were studied by the micropuncture technic. Ventricular fibrillation was characterized by irregular action potentials of varying amplitude. When the individual fibers were in close proximity there was a partial synchronism of these action potentials that was not evident when the fibers were at a distance. During ventricular tachycardia single fiber electrical alternans was frequently observed. This was associated with mechanical alternans, but mechanical alternans occasionally was seen without demonstrable single fiber electrical alternans. Further, in any 1 preparation not all of the cells participated in electrical alternation. These experimental results indicate that alternation of the heart, both electrical and mechanical, may be related to alternate variations in behavior of individual fiber membrane and contractile elements.

SAGALL

**Cranefield, P. F., Hoffman, B. F., and de Carvalho, A. P.: Effects of Acetylcholine on Single Fibers of the Atrioventricular Node.** Circulation Research 7: 19 (Jan.), 1959.

Transmembrane recordings were obtained from fibers of the A-V node. in the rabbit heart during the action of acetylcholine. During total atrioventricular dissociation no block of conduction was noted at the junction between the A-V node and the bundle of His or within fibers of the atrium. Failure of impulse transmission did occur in fibers in the atrial margin of the A-V node. Acetylcholine blockade was associated with slow depolarization, a decreased amplitude in the action potentials, and fragmentation of the action potential into several asynchronous components. The results are believed to support the concept that transmission through the A-V node is decremental.

PAUL

**Cope, F. W.: Elastic Characteristics of Isolated Segments of Human Aortas Under Dynamic Conditions.** J. Appl. Physiol. 14: 55 (Jan.), 1959.

An electronic system was built that provided a continuous plot of pressure versus volume on

the screen of a cathode ray oscilloscope. With this technic a study was made of isolated segments of human aortas which were being continuously expanded and contracted at a frequency and amplitude approximately that found under physiologic conditions. When the pressure-volume curves under dynamic conditions were compared with those static conditions, it was found that the aortic measurements showed a slight change in slope. When the volume of the aorta was changed rapidly and continuously in sinusoidal fashion with pulse pressure and pulse rates maintained in the physiologic range, the resulting pressure-volume curves showed slight but consistent increases in stiffness, compared to pressure-volume curves obtained on the same specimen when inflated stepwise.

RINZLER

**Burch, G., and Hyman, A.: A Study of the Influence of Tropical Weather on Output of Volume Work, and Power by the Right and Left Ventricles of Man at Rest in Bed.** Am. Heart J. 57: 247 (Feb.), 1959.

Five patients without congestive heart failure were studied while at bedrest in the hospital in regard to the output of volume, work, and power by the right and left ventricles. It was found that in the tropical weather during midsummer in New Orleans there was a 37 per cent increase in the mean cardiac output over that in a comfortably cool air-conditioned atmosphere. The calculated time-course curves of the pressure-volume diagram, work, and power were proved to be better indices of cardiac work than the conventionally obtained mean volume of cardiac output. These observations indicate that when it is desired in treatment to maintain the heart at rest, the atmosphere of the patient's room should be cool and comfortable.

SAGALL

**Bondurant, S., and Hickam, J. B.: Circulatory and Pulmonary Effects of Acute Central Vascular Engorgement in Normal Subjects.** Dis. of Chest 35: 83 (Jan.), 1959.

Pulmonary compliance, central venous pressure, and pulmonary vascular density were measured in normal subjects before and during inflation of a G suit and during body immersion in water. Within 30 seconds after suit inflation to 2 psi, compliance decreased, central venous pressure increased and pulmonary vascular density increased maximally. After these maxima were reached, changes in the opposite direction occurred throughout the remainder of the 2-minute period of G suit inflation in all of the parameters. Changes of similar magnitude and direction in pulmonary compliance occurred during immersion in water to the neck and to a greater extent during total body immersion. When peripheral arterial pressure was reduced by administration of hexamethonium there was a smaller increase in compliance with the G suit followed again by the rise toward normal. When the peripheral arterial blood pressure was raised with norepinephrine there was an increase in central venous pressure and a fall in compliance before inflation of the suit, which in turn enhanced these changes initially. The usual return toward normal was not observed in these subjects. Similar changes occurred with immersion of 1 arm in ice water during the studies.

MAXWELL

**Holmgren, A., and Linderholm, H.: Oxygen and Carbon Dioxide Tensions of Arterial Blood during Heavy and Exhaustive Exercises.** Acta physiol. scandinav. 44: 203, 1958.

This study was undertaken to resolve the divergent views on the effect of exercise on arterial blood gas tensions. The subjects were 14 young athletes 19 years of age and younger. The physical working capacity of each subject was assessed on an electrically braked bicycle ergometer. Resting, exercise, and postexercise electrocardiograms were taken. During the test arterial blood was taken by means of a polyethelene catheter introduced into the brachial artery. Samples were taken at rest and during muscular work of defined absolute and relative intensities. The oxygen tension of arterial blood was found to be lower during heavy work than at rest. Exhaustive work caused a further decrease in oxygen tension. Carbon dioxide tension tended to decrease during exhaustive work. The divergent results of other investigators may therefore be due to data obtained at different relative work loads.

RINZLER

**Beavers, W. R., and Covino, B. G.: Relationship of Potassium and Calcium to Hypothermic Ventricular Fibrillation.** J. Appl. Physiol. 14: 60 (Jan.), 1959.

When, under pentobarbital anesthesia, dogs were cooled in ice water to terminus, the incidence of ventricular fibrillation was found to be 96 per cent. Treatment with intravenous

potassium chloride, 150 to 250 mg. per Kg., reduced this incidence to 57 per cent. The administration of ethylene diamine tetracetic acid had only a slight effect on decreasing the incidence of fibrillation. By combining both drugs, the incidence was reduced to 50 per cent.

RINZLER

## PULMONARY DISEASES

**Robin, E. D., Travis, D. M., Bromberg, P. A., Forkner, C. E., Jr., and Tyler, J. M.: Ammonia Excretion by Mammalian Lung.** Science **129**: 270 (Jan. 30), 1959.

Ammonium acetate was infused intravenously into 7 anesthetized dogs, and the concentration of ammonium in the expired air was measured by nesslerization. Calculations of the partial pressure of ammonia in alveolar air and estimations of the theoretical partial pressure in arterial blood were made. The authors point out that demonstration of free ammonia in alveolar air may be taken to indicate that under special circumstances there are significant levels of circulating ammonium. The study of ammonia excretion by the lung may, therefore, make it possible to reassess the quantitative aspects of ammonium metabolism and its relation to hepatic coma.

KARPMAN

**Liljestrand, G.: Chemical Control of the Distribution of the Pulmonary Blood Flow.** Acta physiol. scandinav. **44**: 216, 1959.

Experiments were performed on the isolated and perfused lungs of the cat in order to study the chemical control of pulmonary blood flow. Cannulae were introduced into the trachea, carotid arteries, pulmonary artery, and left atrium. The plastic tube to the pulmonary artery, was connected with a strain-gage manometer. Blood from the lungs passed a recording pH meter. Constriction of pulmonary vessels obtained by raising the carbon dioxide tension of the ventilating gas mixture was mediated by lowering the pH of the blood: a decrease of 0.01 corresponding to a rise in perfusion pressure of about 1 per cent. Ventilation with nitrogen sometimes led to a decrease or an increase in the perfusion pressure. Lactic acid was continuously released from the perfused lungs and this was enhanced by hypoxia. Injections of monoiodoacetic acid abolished or reversed the pressure rise obtained during ventilation with nitrogen.

RINZLER

## ROENTGENOLOGY

**Thurn, P.: Roentgenological Evaluation of Cardiac Efficiency.** Fortschr. Roentgenstr. **90**: 1 (Jan.), 1959.

Cardiac size alone, with the exception of extreme cardiac enlargement, cannot be used in estimating cardiac efficiency. This is especially true of conditions causing increased cardiac filling, such as aortic insufficiency, intracardiac shunts, and arteriovenous aneurysms. In these cases appearance of pulmonary congestion or atrial enlargement is a more sensitive sign of cardiac failure than of left ventricular enlargement. The value of the appearance of pulmonary vessels, vena cava, and pleura in the diagnosis of right, left, or bilateral heart failure is demonstrated with numerous examples.

LEPESCHKIN

**Burgemeister, G., and Rautenburg, H. W. Contribution to the Diagnosis of Persistent Ductus Arteriosus Botalli.** Ztschr. Kreislaufforsch. **48**: 1 (Jan.), 1959.

In 1 patient the catheter could not be made to enter the aorta in spite of repeated catheterizations from the pulmonary artery, but a ductus could be visualized by means of retrograde aortography. In another patient, whose ductus had been ligated previously, the catheter entered the descending aorta in a manner held typical for persistent ductus, but a wide aorticopulmonary communication was found during operation. It is concluded that only direct visualization of the ductus by means of retrograde or transductal aortography can allow definite differentiation between persistent ductus and aorticopulmonary communication or fistula.

LEPESCHKIN

**Burgemeister, G., Rautenburg, H. W., Krienke, E. G., and Kolrep, W.: Indications and Methods of Angiocardiography in Congenital Heart Disease of Children.** Ztschr. Kreislaufforsch. **48**: 8 (Jan.), 1959.

Minute visualization of the cardiovascular congenital anomaly is of great importance for the surgeon; this can be carried out best by means of selective angiocardiography. The anomalies most commonly found in children are discussed in relation to the best method of angiocardiography, location of the catheter and choice of camera or film changer. The dangers of using the method unilaterally are illustrated in a patient with tricuspid stenosis who died in pulmonary edema 2 days after angiocardiography of the right ventricle; this complication could have been prevented by injecting the dye into the right atrium.

LEPESCHKIN

# AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.
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## AHA SCIENTIFIC SESSIONS

About 100 original scientific papers will be presented at the American Heart Association's 32nd annual Scientific Sessions to be held from Friday, October 23 through Sunday, October 25, at Convention Hall, Philadelphia. These presentations will be made during 6 sessions of broad clinical interest sponsored by the Association's Council on Clinical Cardiology and at concurrent special scientific sessions and programs sponsored by other AHA Councils.

The program will also include a session with the American College of Cardiology which this year is conducting its Interim Meeting to coincide with the AHA Scientific Sessions. This will consist of a panel on "Cardiac Resuscitation" to be held jointly with the Council on Clinical Cardiology, on Sunday afternoon, October 25. Heart Association members will participate in the College's popular "Fireside Conferences," on Friday evening, October 23.

In addition, the Association's Council on Arteriosclerosis, formerly the American Society for the Study of Arteriosclerosis, will participate in a panel on "Conflicting Concepts of Atherogenesis" on Sunday morning, as well as in an afternoon program on arteriosclerosis.

Secretary Arthur S. Flemming of the U. S. Department of Health, Education, and Welfare, will be guest speaker at a business luncheon of the Council on Community Service and Education on Saturday, October 24 at the Bellevue Stratford Hotel. His subject is: "The Role of Voluntary Health Associations in Meeting Future Health Needs."

Following is a schedule of other highlights of the three-day Scientific Sessions program:

### *Friday, October 23*

*Morning:* Session on clinical cardiology devoted to a symposium on "Cardiovascular Regulation and its Role in Cardiovascular Disease"; simultaneous sessions on rheumatic fever and congenital heart disease, and on circulation.

*Afternoon:* Presentation of submitted papers of general interest in clinical cardiology; Lewis A. Conner Memorial Lecture, "The Performance of the Heart," by Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago; session on cardiovascular surgery.

### *Saturday, October 24*

*Morning:* Session on clinical cardiology consisting of two symposia: "Recent Developments in Diagnostic Techniques" and "Open Heart Surgery in Acquired Valvular Heart Disease"; simultaneous session on high blood pressure research.

*Afternoon:* Presentation of the Association's Albert Lasker Award; George E. Brown Memorial Lecture, "Circulatory Congestion and Heart Failure," by Ludwig W. Eichna, M.D., Professor of Medicine, New York University College of Medicine; symposium on "Congestive Heart Failure," including a panel, "Treatment of Congestive Heart Failure," and a presentation, "A Useful Life After Heart Failure"; session on basic science; session on cardiovascular surgery.

### *Sunday, October 25*

*Morning:* Panel on "Conflicting Concepts of Atherogenesis"; concurrent session on "Instrumental Methods in Cardiovascular Research."

*Afternoon:* Joint panel with the American College of Cardiology on "Cardiac Resuscitation"; session on arteriosclerosis.

The Scientific Sessions program will also include a session on medical motion pictures, with each film introduced by the author and followed by discussion. A section of scientific and industrial exhibits will also be included. The Heart Association's Annual Dinner will be held on Sunday evening in the Bellevue Stratford Hotel.

### Urge Early Registration

Registration and hotel accommodation forms are now available from the Association. Physicians who register in advance by mail will be sent a complimentary copy of the program booklet containing the abstracts of the proceedings, which will sell for $2.00 at the meeting.

## AHA ASSEMBLY MEETING

Following the Scientific Sessions, the 35th Annual Meeting of the Assembly, delegate body of the Association, will be held on October 26-27 at the Bellevue Stratford Hotel. Six Assembly Panels, in session all day Monday, will discuss: Research; Fund Raising; Relationships and Responsibilities Between National, State and Local Heart Associations; Community Relationships of Heart Associations; Program Activities in Community Service and Education; and Heart Association Organization.

The general session of the Assembly meets on Tuesday morning to review panel recommendations and elect officers and Board members of the Association.

## PUBLISHING DIRECTOR NAMED FOR AHA SCIENTIFIC JOURNALS

The Association has named Alan Baird Hastings as Publishing Director for its 2 scientific journals, *Circulation* and *Circulation Research*, which will be published directly by the AHA beginning January 1960.

## AHA GRANT-IN-AID APPLICATIONS ARE DUE BY NOVEMBER 1

Applications for Heart Association grants-in-aid for the fiscal year beginning July 1, 1960 must be received by the Assistant Medical Director for Research at the AHA National Office, 44 East 23rd Street, New York 10, N. Y., not later than November 1, 1959. The deadline for submitting applications for Research Fellowships and Established Investigatorships was September 15.

All applications for grants-in-aid must be made on forms obtainable from the Association. Grants are made to nonprofit institutions in direct support of a particular investigator for a specific program of research under his direction. Awards are in support of research in the cardiovascular field or basic sciences for periods up to 5 years.

Mr. Hastings, who will have executive responsibility for publication of both journals, has been with Harvard University Press since 1950. During this period, he was also adviser on publications to The McLean Hospital, Belmont, Mass. Previously, he was associated with Columbia University Press, the Council on Foreign Relations and the War Department. Educated at Harvard University, he has done graduate work both at Harvard and the University of Paris.

Under the new arrangement, business communications for the journals may be addressed to Mr. Hastings at the American Heart Association. As in the past, editorial communications for *Circulation* will be received by Herrman Blumgart, M.D., Editor, 330 Brookline Avenue, Boston, and, for *Circulation Research*, by Carl F. Schmidt, M.D., Editor, Laboratory of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia 4, Pa.

## ARTERIOSCLEROSIS COUNCIL MEETING IN CHICAGO

The AHA Council on Arteriosclerosis, formerly the American Society for the Study of Arteriosclerosis, has scheduled its Annual Meeting and business sessions on November 8-9 in Chicago's Hotel Knickerbocker. On Sunday, November 8, Paul Dudley White, M.D. of Boston, will present the G. Lyman Duff Memorial Lecture on the subject "Atheroma and Thrombosis—Major Threats to Our Health Today."

The Council will also participate in the AHA Scientific Sessions, October 23-25 in Philadelphia.

## ARTICLES OF PHYSICIAN INTEREST IN LATEST "HEART BULLETIN"

Several articles of particular interest to the practicing physician are contained in the September-October issue of The Heart Bulletin, sponsored by the AHA in cooperation with the National Heart Institute and the American Academy of General Practice.

Included are: "Regulation of Systemic Vascular Volume and Venous Return by the Sympathetic Nervous System," by John C. Rose, M.D.; "Hypercholesterolemia and Heart Disease," by Louis N. Katz, M.D. and Ruth Pick, M.D.; "Modern Diuretic Therapy: an Aid to Treatment of Various Edematous States," by Ralph V. Ford, M.D.; "Direct Surgical Treatment and Sympathectomy in Obliterative Arterial Disease From Arteriosclerosis," by J. Harold Harrison, M.D.; "Embolism Secondary to Disease of the Mitral Valve: Treatment," Bruce Logue, M.D. and Thomas Dickinson, M.D.; and "Pulmonary Embolism and Infarction," by Brent M. Parker, M.D.

## UNITED FUNDS WOULD DELAY HEART DISEASE CONQUEST SAYS DR. PAUL D. WHITE

Progress toward prevention and more effective control of cardiovascular disease would be seriously delayed by submerging Heart Fund campaigns in local community chests or united funds, Paul Dudley White, M.D., Boston, declared in a statement issued recently through the American Heart Association.

The statement was in reply to efforts being made to force various major national voluntary health agencies to join local federated fund drives. It pointed out that while such community funds serve a useful purpose in meeting local charity and welfare needs, they were "never intended to enter the fields of extensive and intensive scientific research or the training of research workers." Programs in these fields—such as those conducted by the AHA—"are far beyond the scope or ability of the United Fund to support," Dr. White said.

Copies of the statement may be obtained from local Heart Associations or from the American Heart Association.

## MEETINGS CALENDAR

September 28-October 2: American College of Surgeons, Atlantic City. Paul R. Hawley, 40 E. Erie Street, Chicago 11, Ill.

October 14-17: American College of Chest Physicians, Albuquerque, N. Mex., Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

October 19-23: American Public Health Association, Atlantic City. B. F. Mattison, 1790 Broadway, New York 19, N.Y.

**October 23-27: American Heart Association Annual Meeting and Scientific Sessions, Philadelphia. American Heart Association, 44 East 23rd Street, New York 10, N.Y.**

November 2-4: Association of American Medical Colleges, Chicago. Ward Darley, 2530 Ridge Avenue, Evanston, Ill.

November 6-7: Central Society for Clinical Research, Chicago. A. S. Weisberger, 2065 Adelbert Road, Cleveland 6, Ohio.

**November 8-9: American Heart Association's Council on Arteriosclerosis, Chicago. Aaron Kellner, N.Y. Hospital, 525 E. 68th Street, New York 21, N.Y.**

November 10-12: Conference on Electrical Techniques in Medicine and Biology, Philadelphia. Herman P. Schwan, University of Pennsylvania, Philadelphia, Pa.

**November 20-21: AHA Council on High Blood Pressure Research, Cleveland. Mrs. J. Bruner, Cleveland Area Heart Society, 1689 E. 115th Street, Cleveland, Ohio.**

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F ɔruary 3-6: American College of Radiology, ew Orleans. William C. Stronach, 20 N. Vacker Drive, Chicago 6, Ill.

F ɔruary 18-20: Central Surgical Association, hicago. Angus D. McLachlin, Victoria Hosɔital, London, Ontario, Canada.

M rch 13-18: National Health Forum, Miami. hilip E. Ryan, National Health Council, 1790 Broadway, New York 19, N.Y.

M ɹrch 19-24: American Academy of General Practice, Philadelphia. Mac F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.

M ɹrch 21-24: Southeastern Surgical Congress, New Orleans. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga.

1960 **ABROAD**

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Avenue, New York 22, N.Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmasse, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

September 18-25: European Congress of Cardiology, Rome. Secretariat, Clinica Medica, University of Rome, Italy.

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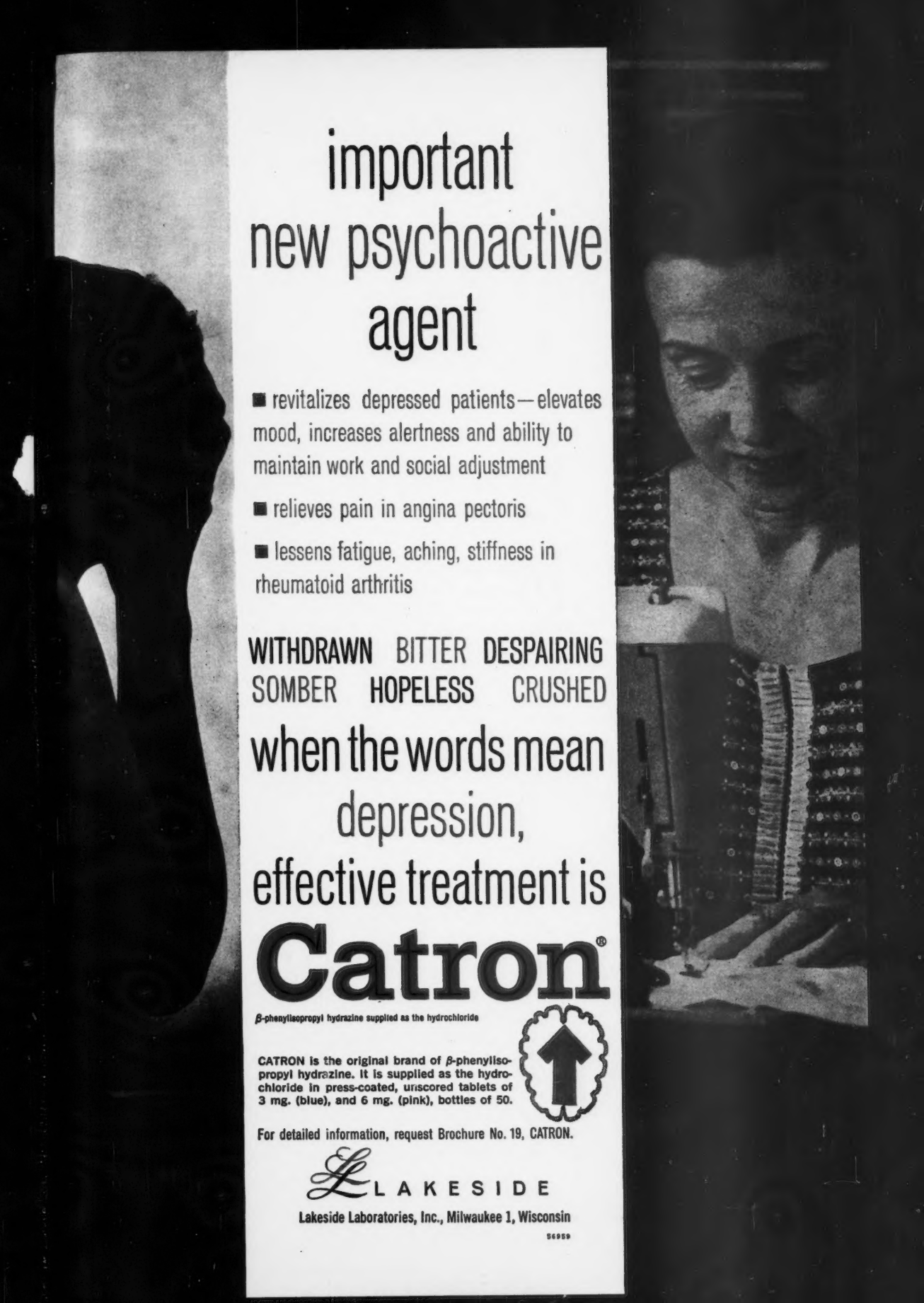

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